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THE RELATIONS BETWEEN THE LYMPHATICS AND THE CONNECTIVE TISSUE.

By W. G. MacCallum,

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The relation between the lymphatics and the tissue in which they lie and more especially the relations with the connective tissue have long been the subject of discussion. Active interest seems to have arisen, as is often the case, at intervals, in this instance, intervals of thirty years, so that while in the third decade of the past century much was written by Panizza,[1] Lauth,[2] Cruveilhier,[3] and others, a lull occurred until 1862 when v. Recklinghausen's[4] publication of the results of his investigations with the aid of his silver method again fired the enthusiasm of a group of workers, some of whom fell in with his ideas, while others opposed them. This period of activity, lasting many years, also subsided into a quietude only recently broken by the work of Ranvier.[5]

Up to v. Recklinghausen's publications various conjectures as to the possibility of connection of lymphatics with the blood vessels, etc., had been pretty well settled by the injections of Teichmann[6] and others, but as to the nature of the walls there was still doubt, for His[7] expressed his opinion that there were no walls, but that the canals were merely excavated in the tissue. He described the lymphatics in the tadpole's tail with a lining of cells with solid processes, and even states that such a cell might alone form the prolongation of the vessel but never suggested that they formed a wall. Then in 1862 came the monograph of v. Recklinghausen in which, in studies made with the aid of silver staining of tendons and the diaphragm of guinea-pigs and various tissues of frogs, he concluded that the closely anastomosing network of lymphatic capillaries, which he describes very accurately, are lined by a single definite thin layer of flat polygonal endothelial cells whose margins are stained black with the silver. These walls are, however, in a sense incomplete, inasmuch as the lymphatic canals are in much closer relation with the adjacent tissue from the presence of fine channels running among the cells of this tissue and opening directly into the endothelial-lined lymphatics through gaps

[1] Panizza, Sopra il sistema linfatico dei rettili. Pavia, 1833.

[2] Lauth, Essai sur les vaisseaux lymphatiques. Strasbourg, 1824.

[3] Cruveilhier, Anat. descr., T. i, ii, 1835.

[4] v. Recklinghausen, Die Lymphgefässe und ihre Beziehung zur Bindegewebe, Berlin, 1862.

[5] Ranvier, Archives d'Anatomie Microscopique, T. i, p. 137–152. Paris, 1897.

[6] Teichmann, Das Saugadersystem vom anatomischen Standpunkte. Leipzig, 1861.

[7] His, Zeitschr. f. Wiss. Zool., Bd. xii, 1863.

in their walls. Such "*saftkanälchen*" (lymph-canaliculi) he demonstrates as clear spaces apparently continuous with the clear space representing the lymph channel in specimens prepared by immersing the fresh tissue—diaphragmatic tendon, etc.—in a solution of silver nitrate. For the sake of clearness one of his figures is reproduced (Fig. 1). By this method lymph-canaliculi could be demonstrated in all varieties of connective tissues and the apparent connection of these clear areas with the clear areas representing the lymphatics was considered proof of their continuity as spaces, although all efforts to inject them failed.

His,[8] who had previously employed this method in the study of other tissues, was struck and delighted with the clearness of the picture of endothelium thus obtained but

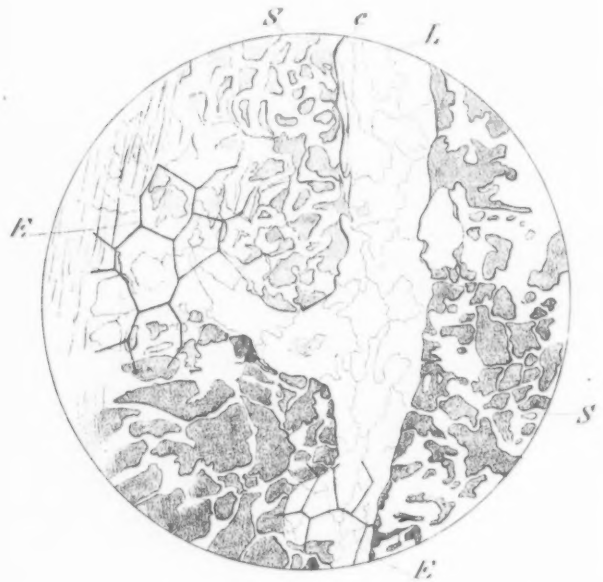

FIG. 1.—From v. Recklinghausen's "Lymphgefässe und ihre Beziehung zum Bindegewebe", Taf. II, Fig. 1. Silver preparation of the uppermost layer of the centrum tendineum of the diaphragm (thoracic surface) of a guinea-pig.

L. Lymphatic-vessel, S. Lymph-canaliculi, c. Outlines of the epithelial cells of the lymphatic vessel, E. Outlines of remaining epithelium of the serosa.

criticised the conclusions of v. Recklinghausen inasmuch as he thought the lymph-canaliculi were an error, that they represented merely the over- and underlying cells which may be stained with silver by treating the diaphragm with strong salt solution after the silver.

Schweigger-Seidel and Dogiel,[9] also writing from Ludwig's laboratory, found no confirmation of the idea of lymph-canaliculi communicating with the lymph channels but thought these appearances due possibly to vacuolation of the cement substance.

Teichmann was one of the earliest defenders of the idea of the complete nature of the walls of the lymphatic vessels, basing his conclusions on the extensive injections which he made. Neumann[10] similarly holds strongly to this idea. Recently Ranvier,[11] injecting the ear tissues in white rats, finds the lymphatic vessels to end blindly and from these and other experiments deduces the idea that the lymphatic system is produced by a long-continued sprouting of blind tubules from the blood vessels beginning at the point of juncture of the thoracic duct and the vein.*

But still all the text-books are full of the idea of tissue spaces in direct connection with the lymphatic radicles and really uniting to form these radicles; whether they are lined with endothelium or not is left undecided but it is suggested that here and there, there are endothelial cells in such spaces. The fluids circulating in the tissues are supposed to be in these spaces and to be thus directly continuous with the fluid in the lymphatics and indirectly with the blood. Wandering cells are supposed to lurk in these spaces and to have ready access to the lymph channels through their porous walls.

It was with the idea of determining if possible the nature of these relations between the channels and the surrounding tissue that the following study was begun, at the suggestion of Professor Marchand in his laboratory in Leipzig and continued in Baltimore.

It was found that the lymphatics could be readily demonstrated by interstitial injections by means of a fine hypodermic syringe in the skin of embryo pigs which were also the most easily obtained of all animals and although the results have been controlled by experiments with other tissues this was adopted temporarily at least as material for observation.

It is well known that in making such cutaneous injections if one passes the needle through the skin into the subcutaneous tissue a great globule of the injection mass forms at the point and no vessels of any sort are injected. If, on the other hand, the needle is inserted too superficially the injection mass bursts out in a vesicle which elevates the epidermis. If, however, the point of the needle is pushed into the denser translucent skin itself and then withdrawn a very little, pressure on the piston will force the injection mass into the lymphatic vessels which spread themselves out as an injected network of extreme delicacy and beauty. In such injections it sometimes happens that the blood vessels of the skin are entered and injected but this occurrence is not very common. An injection of the blood vessels is very

[8] His, Zeitschr. f. Wiss. Zool., Bd. xiii, 1864.

[9] Schweigger-Seidel und Dogiel, Arbeit aus der Physiol. Anstalt. Leipzig, 1866.

[10] Neumann, Zur Kenntniss der Lymphgefässe der Haut. Wien, 1873.

[11] Ranvier, Loc cit.

*Since this paper was written, Dr. Sabin has described (American Journal of Anatomy, 1901–02, vol. 1, p. 367) the whole development of the lymphatic system from a bud from the vein wall, which shows that Ranvier's surmise was in fact very near the truth. Her work further confirms almost all the results expressed in this paper.

easily recognized macroscopically as it has nothing of the intimate anastomoses which go to form the dense network seen when the lymphatics are injected. Naturally the pressure used in injecting must be very slight as otherwise the delicate lymphatics may be ruptured. In the embryo pig the most beautiful injections may perhaps be obtained in the skin of those measuring from 60-150 mm.; the younger pigs are rather too delicate for manipulation and in the older ones the induration of the skin which comes on toward the completion of gestation renders it difficult to inject any considerable area. Any portion of the skin may be injected, that over the rump and hind legs is perhaps the most favorable. Often in such injections when the cutaneous network is well distended, long, wide and fairly straight trunks may suddenly become marked out, running from the skin to the inguinal or axillary region and evidently meeting there with the glands in those regions; indeed, in very young pigs it has sometimes been possible on inserting the needle deep into the inguinal region at the point where the glands should be, to inject the cutaneous network over the whole side of the pig.

It is not the purpose of this paper to describe the gross relations of the lymphatic channels to the skin, etc., suffice it to say that there is a deeper network of wide anastomosing channels lying in the lower level of the skin from which branches of a narrower caliber rise toward the surface and divide to ramify in these more superficial levels. The channels forming the lower network have the curious pear-shaped segments, so often represented in text-books, which give rise to the somewhat beaded appearance seen in the injected specimens. These are often enough seen to be branched so that there are two or more of the widened and rounded ends and from each of these there springs a new segment or sometimes two, starting as a narrow tube and widening out in turn to form again a bulbous end from which spring new narrow stems. At the bulbous end at the point of origin of the next segment the communication of the first with the second segment is further narrowed by the presence of a valve-like annular septum formed of a double plate of cells which project into the lumen of the canal. The valve action of such an annular septum seems not to be very efficient in either direction, for if the injection be carried out under the microscope the fluid may be seen to pass in either direction. The structures of these valves will be discussed more fully later. The branches springing upward toward the epidermis have not been observed to have this curious segmentation.

These details could be readily observed by tearing off the skin and clearing it for examination microscopically; especially satisfactory is the examination of such objects with the new Greenough stereoscopic microscope.

The tissue in which these vessels lie is seen in sections to be the connective-tissue corium; neither in the underlying much looser subcutaneous tissue nor in the epidermal layer are any injected branches found. The corium is composed of a mass of cells lying in a rich intercellular substance in which run also thin-walled blood vessels. The blood vessels are distinguished from the lymph vessels described above by the stoutness of the cells forming their walls which are very conspicuous even when the lumen is collapsed, by the parallelism of their walls and often by their content of blood (Fig. 2).

The connective-tissue cells are fairly homogeneous, in form they are generally elongated and somewhat fusiform or cylindrical, but from both ends and sometimes the side there spring most numerous protoplasmic processes which are long and rather wavy and run about, twisting among those of the adjacent cells. The cell body is fairly granular and deeply staining. The nucleus, which is elliptical or oval,

FIG. 2.—Section of skin of embryo pig showing a blood vessel and a lymph vessel lying in the connective tissue.

generally shows a nucleolus and in such tissue karyokinetic figures are found with great frequency.

The intercellular substance is homogeneous and is apparently a fluid or semifluid material. It takes an indefinite greyish-pink color in sections stained with hæmatoxylin and eosin.

The blood vessels are very conspicuous objects in such preparations. They run in general toward the surface where they branch out tree-like; everywhere their walls are formed of quite stout endothelial cells with vesicular but deeply staining nuclei. The cell bodies are not very large, so that the nuclei are crowded together, giving the capillary wall a very solid appearance. The strength of these walls may be put to the test by a forcible injection which leaves them distended with the injection mass but without any leakages or

extravasation. In sections the vessels are often empty and collapsed but generally contain some blood.

In sharp contrast with these appear the lymphatic vessels. They may be observed in frozen and unstained sections (Fig. 2), or even in the freshly torn-off skin itself as canals which stand open and constitute wide gaps in the section or clear bands in the complete skin. By staining such a frozen section with hæmatoxylin and eosin the channels are found to be lined by cells whose cell body is quite invisible *en-face* the protoplasm being so clear but whose nuclei are rounded or elliptical and flattened. These nuclei are easily distinguished from those of the surrounding cells by this spread-out flattened appearance which contrasts strikingly with the somewhat fusiform or cylindrical and hence deeper staining nuclei of the others. The contrast between the perfectly transparent cell body without apparent processes and the granular deeply-staining protoplasm and myriad processes of the connective-tissue cells is perhaps even more imposing. If now we immerse a portion of tissue containing such channels in a solution of silver nitrate these lining cells are marked out with extreme clearness, the outlines or intercellular lines being blackened. This object is obtained with much greater clearness by an injection of the canals with weak silver nitrate solution. From this procedure together with the stained sections we have no trouble in concluding that the endothelial cells are irregularly polygonal flat scale-like structures, each with a vesicular nucleus which accommodates itself to the flattening of the cell in being also flattened. The processes of the adjacent connective-tissue cells impinge directly upon these endothelial cells, and indeed in sections which show the outer surface of such cells, there are generally to be seen bits of overlying cell processes. Still it seems that with very few if any exceptions the endothelial cells give off no processes of their own to the surrounding network.

We have then several features to consider in the structure of these channels; first from an anatomical point of view, and later in the light of their behavior under certain normal and abnormal conditions. It has been stated that the lymphatic channels have not complete walls but that they are in free communication with certain ramifying spaces in the tissue ("saftkanälchen") through pores in their walls. To control this statement is one important necessity. It is necessary further to determine if possible in how far the lining cells of these channels are permanently differentiated from the remaining cells. The mode of growth of the lymphatics must be determined. Further problems will arise in the less purely anatomical consideration of these structures.

von Recklinghausen's work was based almost entirely on the preparations obtained by simply immersing various tissues in a solution of silver nitrate; of these the diaphragm of the guinea-pig seemed to offer an especially convincing picture and, indeed, one does see on brushing off the peritoneal and pleural endothelium and then treating with silver a network of vessels lying in a curiously stained tissue. Each vessel is lined with endothelial cells which are sharply outlined in black; the cell bodies are left quite unstained and the vessels therefore stand out as a clear band in the relatively darkly stained tissue, although it is overlaid by a thin layer of this tissue. The irregularity in the appearance of the staining substance is due to the presence of ramifying unstained areas which seem to be quite as truly spaces, and as they run to the lymphatics seem to be in direct connection with them; between such spaces is a brown granular ground substance. Further than this v. Recklinghausen did not go but stated definitely that these clear areas were the tissue spaces or *saftkanälchen* and that they undoubtedly opened into the lymph channels.

More careful study of such preparations does not, however, lead convincingly to such conclusions. By careful focussing it can generally be observed that the "*saftkanälchen*" are on a different level from the lymph channels; moreover the appearance of actual communication of such spaces with the channels is not nearly so frequent as might be supposed from first impressions, and when it does occur it is generally at a point where the outline of the channel is formed in the optical plane, not by the well-stained endothelial line or margin of the endothelial cells, but by the perfectly transparent curved cell body, so that any transparent body in contact with it would seem to be a space in communication with the cavity of the channel. Torn specimens sometimes show the lymph-canaliculi very well but show the torn end of a stained lymph channel projecting from a lower layer of tissue and quite free and independent of them. In one such specimen one could focus on the tissue with its irregular brown staining and apparent spaces and a little lower one reached the well-defined channel projecting free as a complete tube from the margin of the torn diaphragm: a lower focus still again showed tissue with the lymph-canaliculi.

Sections of such a diaphragm mounted without further treatment show a blackish deposit among and outlining the connective-tissue cells and even the muscle bundles, but not often penetrating to the central portion of the diaphragm. The lymphatics appear as sharply outlined tubes lying just on the surface of the musculature in the subserous fibrous tissue. In carefully studied serial sections no openings in the walls of these tubes could ever be seen.

These sections made both in longitudinal and vertical directions showed more than a negative result, however, for when stained with a nuclear stain the clear spaces or "*saftkanälchen*" so sharply outlined with blackish granules proved each to contain a nucleus and protoplasmic cell body. In a word, the silver acts here exactly as in the walls of the lymph channels and stains with its black precipitate the margins of the cells and intercellular substance and the picture of wide lymph channels with communicating lymph-canaliculi represents nothing more than the lymph channels with the unstained neighboring cells impinging upon them and standing out as clear spaces in the mass of irregularly stained intercellular and fibrillar substance (Fig. 3).

This is especially well seen in flat sections of the skin of fœtal pigs treated with silver in which the beautifully branching cells described above are picked out with a margin of silver which marks out all the fine fibrillæ with borders of infinitesimal granules; lying near the gaping lymph channels they seem like finely-ramifying spaces, sometimes when near enough even appearing to open into the lymph channel. A nuclear and protoplasmic stain, however, leaves no doubt as to the true state of affairs, and the smooth-walled lymphatic is left coursing through a mass of cells and stained intercellular substance.

v. Recklinghausen seems not to have injected the lymphatics with the silver solution. Such an injection without further treatment with silver gives in the diaphragm of the guinea-pig an exquisite network of smooth walled vessels with a quite perfect lining of tessellated endothelial cells. The intervening and surrounding tissue is not stained. v. Recklinghausen did inject colored substances but never could he induce any of them to enter the lymph-canaliculi,

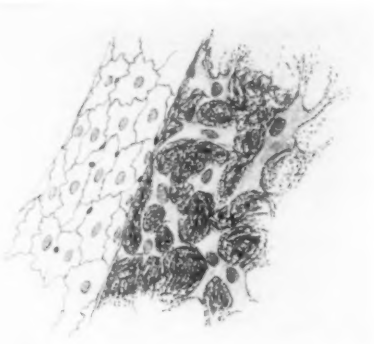

FIG. 3.—Silver preparation from skin of embryo pig. The nuclear stain makes clear the nature of apparent spaces impinging on the lymph vessel.

although as he pictures them the mouths are quite wide. So also various others produced an injection of the diaphragmatic lymphatics by introducing colored substances into the peritoneal cavity of the living animal but always the fact that no structures resembling lymph-canaliculi were injected was most striking. Arnold[12] claims to have injected such spaces in the frog and even in an œdematous frog's leg to have forced injection material from the blood vessels into the lymph vessels by their mediation, but no one has injected them in the higher animals.

From all this it appears that in mammals, at least, the apparent spaces produced by treatment with silver nitrate and named *saftkanälchen* do not represent spaces, are not to be injected or in any other way to be demonstrated to be in connection with the lymphatics, but are cells whose outline has been stained with the silver which is also precipitated in the material lying between them.

[12] Arnold, Virchow's Archiv, 1875, Bd. lxii, 157.

Finally, it would appear that if, as v. Recklinghausen will have it, the tissue spaces are in wide free communication with the lymphatics, in œdema of the tissues the widening of the tissue spaces must be associated with similar widening of their communications with the lymphatics and of the lymphatics themselves in the œdematous area. Injections, however, of the lymphatics in a very œdematous skin or in such tissue as the extremely œdematous gall bladder found in a case of acute nephritis, gave a network of vessels quite as sharply outlined and quite as narrow and free from extravasation as any injection of normal tissue. Indeed, one could not distinguish the network in the œdematous tissue from the normal. Evidently then the tissue spaces are to that extent independent of the lymph channels.

Of course it is not meant to be understood that it is in any way thought that tissue spaces do not exist. It is not conceivable that tissue elements should be so firmly bound together as not to be separable and the simple condition of

FIG. 4.—An extravasation of injection mass through the wall of the lymphatic.

œdema demonstrates with all clearness the separation of the tissue elements with the production of wide tissue spaces. It does seem, however, that these from their nature are variable and instead of being definite cavities lined with endothelium or in direct permanent communication with the lymphatics are dependent for their temporary existence on the separation of the cells and intercellular substances. The mere examination of specimens injected with silver or merely stained in silver is enough to convince one that there are at least no spaces completely or incompletely lined to be found in connection with the lymphatics.

That tissue spaces not in free communication with the lymphatics are abundant seems, however, to be proven by a mode of procedure first employed by Juckuff.[13] He injected paraffin liquid at a low temperature; or, better still, a mixture of paraffin and petroleum ether which remaining fluid

[13] Juckuff, Archiv f. Experimentelle Pathologie u. Pharmakologie, 1893, Bd. 32, p. 124–159.

during injection slowly lost the ether afterward. Such an oily material was injected into the subcutaneous tissues where it formed a great bulla, but if the animal were allowed to live for days or weeks a gradual distribution of the paraffin took place, apparently largely influenced by gravity and the muscular movements, so that it was found on the death of the animal widely distributed and in tissues far distant from the point of injection. Juckuff found that only after a very long time was any trace of the paraffin found in the lymphatics or lymph glands. Repetitions of his experiments have been entirely confirmatory of his results, one obtains as it were a paraffin œdema; masses of paraffin are found in regions of the subcutaneous tissue far distant from the point of injection and sections of such masses with the surrounding tissue show that the masses themselves, consisting apparently of pure paraffin, are in reality the very finely divided areolar tissue between the elements of which lies the paraffin. It is merely a most extensive separation of the cellular elements by the paraffin. The lymphatic trunks draining such a region were not injected nor did the lymphatic glands show a filling up with the paraffin; apparently evidencing the possibility of the injection of the tissue spaces with a fluid without the lymphatics.

We have still to determine whether or not the walls of these lymph channels are quite complete. When injected with silver nitrate the endothelial lining behaves exactly as does that of the blood vessels, and we find in the endothelial margins dots and sometimes circles of black silver deposit which suggest of course that holes have been present and have been the seat of a more abundant silver deposit than usual, or at least that a widening or accumulation of the intercellular material has been present. Satisfactory explanation of these stigmata and stomata is difficult to find. They are often mere dots in the silver line; often much larger round black masses; sometimes they form ring-shaped widening of the lines and then they look more like holes (stomata), still careful examination will generally reveal granules of black within such rings, or even the much attenuated margin of the cell coursing through the center to complete the original silver line interrupted by the ring. So, too, such dots and rings most often with enclosed granules can frequently be found on the body of the endothelial cell away from the marginal line. Injections of Berlin-blue following the silver show no tendency to pass through these rings, and indeed if extravasations of the blue occur they are quite as likely to be at some other point, and, on the other hand, injections of silver nitrate following injections of blue show no especial tendency to produce such dots and rings at the points where extravasation of the blue has occurred.

From these facts it seems fairly certain that such silver markings do not represent holes or any constant structural peculiarity in the walls but are rather accidental precipitations of the silver without especial relation to the anatomical structure.

Efforts were made to observe the endothelial walls in stained sections and this was found to be readily possible in serial sections made parallel to the flat surface of the fœtal skin. Such sections were stained with the ordinary stains and also with the osmic-tannic stain of Kolossow, but although very many walls were searched through, no evidence of pores or holes could be found; sometimes small irregular rents were seen but their inconstancy and irregularity in shape and size forced one to the conclusion that they were merely artefacts.

Mention was made above of extravasation which occurred in injected specimens, and indeed it is almost impossible even with the very lowest pressure to obtain injections entirely without extravasations. When silver is used, as described above, for injection of the diaphragm, extravasations do occur here and there quite irregularly. They permeate the surrounding tissues and at such a point the sharply outlined lymph channel is seen to enter a rounded blur of stained tissue in which the lymph-canaliculi can be readily seen and as readily tested, as described above. Injections with Berlin-blue are especially likely to give rise to extravasations and one often finds the network of injected lymph channels made up in large part of shaggy tubules whose definite outline is almost completely destroyed by the tufted extravasations which are ranged along the margins. This seems to be the most difficult objection to explain away among those brought against the idea of the closed nature of the endothelial wall. Are not these tufted extravasations, it might be asked, merely injections of the lymph-canaliculi through the preformed pores in the walls of the lymphatics? Sections of such injected tissue show, however, pretty definitely that the blue outside of the vessels is in quite irregular masses and is lying quite without respect for the cells of the adjacent tissue which it has pushed aside, sometimes causing considerable damage and destruction of the tissue and often surrounding and including cells (Fig. 4). In other specimens the injection has been so rapid that the blue remains in solution long enough to diffuse in the tissue outside the vessel and cause a blurred blue staining. When it appears as a definite mass outside the lymph channels it is generally continuous with that still inside the main channel by a stalk as it were, and this can in most instances be traced through a definite rent in the vessel wall, which shows then a corresponding bulging (Fig. 4). The picture is quite obviously that which one could produce by forcibly driving the fluid injection through the delicate wall, bulging and rupturing it and invading and pushing aside the tissue outside. In order to control this, similar injections of aqueous Berlin-blue were made under the microscope. This was accomplished by tearing off a piece of skin and laying it epidermis down on a slide on the stage of the microscope and injecting with a hypodermic syringe while observing the entrance of the injection mass. Even before any injection was begun the lymphatics could be made out as clear bands in the tissue quite sharply outlined from the surroundings. On beginning the injection the blue could be seen running along in these channels as a central blue stream, gradually

widening to fill the whole channel; often on account of the extreme richness of the anastomoses the blue could be seen in a given field of the microscope approaching from opposite directions. The valves of the lymph channels seemed to exercise no particular directing influence, for the blue passed from the narrow into the bulbous ends of the segments, or the other way, apparently with equal facility. When the current passed from the tapered end into the widened pear-shaped end of the next segment it was generally seen to eddy about as a central blue current with colorless marginal zones, finally filling the whole channel.

With very low pressure such an injection could be seen to penetrate a certain region of the network without distending the tubules and leaving them as quite smooth-walled canals sharply injected with blue; long continuation or increase of the pressure, however, produced an evident distension of the vessels which nevertheless still remained sharply outlined until suddenly with the continuance of the pressure these could be seen to burst from the wall a bush-like tuft of blue, then another and another quite irregularly; sometimes only one in a whole segment; sometimes so many that the channels were quite covered over with them. The sudden explosive appearance of these tufts seemed to be fairly conclusive evidence of their being traumatic in their nature; forcible extravasations from bursting of the wall rather than the injection of preformed channels. By pressure on a coverslip placed over such an injected specimen, all of the injecting fluid could be pressed out of the lumina of the actual lymph channels, leaving the extravasations unchanged as a sort of blue fringe along the clear empty canals. This surely would not occur if these masses of blue were in communication with that in the lymphatic by preformed channels. In such a case the injection should be squeezed out of one part of the injected system with practically the same ease as from the other parts.

The anatomical evidence then seems to show that the walls of the lymphatics, although delicate in the extreme and easily ruptured by a pressure in injecting which could not rupture the most delicate blood vessel, are still possessed of a complete endothelial lining which shows no pores

FIG. 5.—Sprouting ends of a lymphatic vessel.

FIG.. 6.—Sprouting strand of endothelial cells forming the prolongation of a lymphatic vessel.

or open communication with the surrounding tissue, but is practically analogous with the lining of the blood vessels.

Klein,[14] in his atlas of histology, briefly stated his belief that the lymphatics were developed in much the manner described for the blood vessels, i. e. by the sprouting and hollowing out of endothelial cells. Nowhere else except for the observation of His on the tadpole's tail have I been able to find any expression of opinion as to this point. The thing itself, however, admits of demonstration and the pictures one obtains in the study of these growing points are very beautiful. In sections of the skin of fœtal pigs they can perhaps be seen to best advantage. Here one can sometimes trace the ascending branches of fine caliber from the deeper-lying network into the superficial layers to their ends.

Fig. 7.—Bridge formed by a single row of endothelial cells, connecting two lymphatic vessels.

These ends, instead of being blunt blind structures, taper gradually until the injection mass is lost in a fine filament bordered by two or more relatively thick endothelial cells; sometimes the extreme point is formed by a single cell which sends its long process further on in the direction of the vessel. Such instances of sprouting ends, filled nearly to their points with the injection mass and prolonged by budding cells, often showing mitotic figures, are frequently to be found (Fig. 5).

In other places it seems as if the point of the injected mass corresponds not with the end of the vessel but rather with the point beyond which the vessel is not yet opened, that is one can sometimes trace in sections the sprouting endothelial cells in strands and lines beyond the end of the injection (Fig. 6).

This was the basis of a rather speculative observation among the notes made at the time these sections were studied. It seems probable that the *anlage* for the lymph network is much more extensive than that which can be injected and that this *anlage* forms a series of sprouting bands of parallel rows of cells perhaps easily separable so as to form a lumen; often only single, i. e. not yet divided longitudinally. It differs thus from the *anlage* of the blood system in not being subjected to a pressure which forces apart the cells as soon as possible, producing a lumen.

This process is often illustrated in the formation of bridges or anastomoses between lymph channels, as in Fig. 7, in which the potential channel between the two large injected trunks is as yet composed of only a single row of cells.

The formation of lateral branches by the sprouting of swollen and dividing endothelial cells can be frequently observed; sometimes one can actually observe the hollowing out of a single cell in the earliest stages but oftenest the lumen is formed between the two cells, products of division of a sprouting cell (Figs. 4 and 5).

The process of growth of the lymphatics is thus in every respect analogous with that of the blood vessels with the exception perhaps of the lack of a considerable distending pressure.

As to the question of the specificity of the endothelial cells very little can be definitely stated. There is certainly a morphological differentiation at a very early stage and one does not escape the impression that the differentiation visible thus early is more than a morphological one and that these cells retain their endothelial nature as distinguished from the surrounding connective-tissue cells throughout all the processes of proliferation and development through which they go.

Objections to the idea of the closed nature of the lymphatics have been raised on the ground that their power of taking up solid bodies could not be explained except by the assumption that holes were present in the walls. Thus the

[14] Klein and Smith, Atlas of Histology, 1879–80.

granular matter introduced in tattooing is well known to be gradually carried along the lymphatics and deposited in the appurtenant lymph glands; and similarly any insoluble granular substance distributed in a wound or on a raw surface is to a greater or less extent taken up by the lymphatics. A classical example is the anthracotic pigmentation of the bronchial lymph glands. In no place, however, does it seem inevitable that we should call in the aid of hypothetical pores in the walls, not only because such pores would probably not be effective in aiding the entrance of solid bodies but more especially because there is much evidence to show that the whole process of taking up and transporting such granular material is carried out by the agency of cells which by their independent motility can leave or enter either lymph or blood vessels. That such phagocytism is extremely vigorous and rapid has been demonstrated again and again, and Thoma[15] has actually observed the transmigration of leucocytes from the blood vessels into the lymphatic channels. As Ponfick[16] states, it is wonderful with what rapidity granular material, such as cinnabar, injected into the circulating blood, is engulfed by cells.

If one observes the mesenteric vessels of a frog while injecting cinnabar into the lateral abdominal vein in small quantity the red granules are seen to float free in the blood current only for a very few minutes, generally less than five, then gradually all the granules are found to be floating along surrounded by a mass of translucent protoplasm which represents the body of one or of several leucocytes which have acted as phagocytes. Such leucocyte masses with central pigment block may float in the current for a long time, finally often sticking in some small vessel. Single leucocytes with a pigment granule may emigrate from the vessel and settle themselves somewhere in the tissue; probably a transfer of the pigment to fixed tissue elements, such as the endothelial cells of the spleen and bone-marrow, soon occurs. We have therefore little reason to believe that free granular matter would be left to find its way unaided into the lymphatics; far more probable, in fact almost unavoidable, is the idea that it is carried in by phagocytic cells.

Injection of granular pigment into the subcutaneous tissue of rabbits showed, after a number of days when the rabbits were killed, pigment in the neighboring lymph glands and strewn along the lymphatic trunk in the line of these glands. Sections of such a trunk and gland showed relatively little free pigment; almost all the granules were enclosed in cells.

The injection of carmine in solution into the blood of living animals produces an injection of the lymphatics of the mesentery accompanying the blood vessels. In such a case the carmine seen in the lymphatics is granular but this is possibly from subsequent precipitation. Such experiments seem not especially instructive because one cannot be sure that the carmine does not remain in solution and in the transfusion of solutions through the walls of vessels there is no difficulty.

The writer looks forward to a continuation of the work on this theme in the study of the conditions existing in various other tissues and organs and especially in the application of the results to the study of various pathological processes.

[15] Thoma, Die Ueberwanderung farblosen Blutkörper von dem Blut in das Lymphgefasssystem. Heidelberg, 1873.

[16] Ponfick, Virchow's Archiv, 1873, Bd. xlviii, p. 203.

It is a pleasant duty to write here an expression of thanks to Prof. Marchand for the suggestion of the subject for investigation and for the help which he gave while it was being carried on in his laboratory.

THE ACCURACY OF CERTAIN CLINICAL METHODS.

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In the opening address of a recent German medical congress, its president, comparing the instruments used in the diagnosis of disease at the beginning of the nineteenth century with those which the scientific inventor and the inventor of scientific instruments of to-day claim are necessary, said, "then could the practitioner say with the old philosopher Bias, 'Omnia mea mecum porto,' or, with greater truth, 'nihil mecum porto,' for he had to rely on his five unaided senses—now a Hercules could not carry all the appliances, even the so-called transportable ones, which in diagnosis are at our disposal, to say nothing of those found only in clinics and laboratories." This which is true of physical apparatus is even more so of the clinical and biological knowledge at the disposal of the practitioner of to-day. Then were used the simplest chemical tests, among which taste was not of least importance; now a person would needs have encyclopedic knowledge to measure up to the standards of the specialists in the various branches of science which have advanced medicine so markedly during this century. The well-trained doctor of to-day usually has, as firm foundation, thorough training in one of these sciences; either he was a well-trained chemist, or a well-trained physiologist, or path-

ologist before he began to specialize in clinical medicine; and nearly every one whatever his training may be likes to be considered well read in one of these or kindred subjects, although to keep up in one branch is hard, even for the specialist in that department; and especially is that true of chemistry. But many desire not only to be well up in clinical chemistry, e. g., but to contribute to the progress of that science, and it is with the hope of aiding some of these that this paper is written.

In the course in clinical chemistry and microscopy given at the Johns Hopkins University the following plan has been adopted. With each instrument of importance and each quantitative method of value the student must not only be familiar, but in the use of them, skillful. In the chemistry courses required for admission to this medical school each student has learned the principle on which most of these methods rest, and in most cases has already used these same methods. In the course in physiological chemistry the student learns the quantitative methods of that branch of chemistry, hence the course in clinical chemistry may teach no new method. It does, however, try to train the student in these methods until his work is accurate. The need of this is self-evident. There is a great deal of difference between knowing how to do a thing and the ability to do it well. During their fourth year the students as clinical clerks must use these methods and then is no time to practice. Since the use of thirteen blood instruments and about that number of methods of quantitative determination of various bodies in the urine and gastric contents are to be thus practiced, the work required is not small; and this is really the minor part of the course, since it is in addition to a great deal of qualitative work, which is new, and the examination of many specimens of various nature. The class works in pairs. The blood instruments are passed from one pair to another outside of class hours. The quantitative chemical work is done in class hours, enough apparatus being provided that the whole class may work at the same time. These pairs work independently and hand in their written results. These are tabulated, and the work is repeated on other days, usually three in all, until the results agree satisfactorily.

To publish the results of such work may at first glance seem of doubtful value, for not only is one method under examination, but at least thirty different sets of apparatus, and the chemical training and personal equation of a class of sixty different students. But therein lies the value of such tables of results for the practitioner who wishes to follow, for instance, the phosphoric acid in a series of cases: he must use still another set of instruments; he also has a personal equation, and I very much doubt that his skill will surpass that of two of our students who have used this method at least two or three times before (we shall not publish their first results) and whose pride is aroused that their results shall be within the limits accepted as satisfactory. They seldom know what answer their neighbors are getting, but each one sees the error in technic that his partner makes and insists that that step shall be repeated.

If it be asked what practitioners have the time and inclination to do such work, we answer many, judging from the interest they as visitors and graduate students take in these subjects.

That the worker should have some idea of the accuracy of a method he wishes to use, also of his accuracy as a worker, is most important. Absolute accuracy is still an ideal in chemistry, but the antithesis of absolute accuracy is, I am afraid, "clinical accuracy." By clinical accuracy we mean that taught in many text-books of clinical chemistry, that advertised as attainable by some clinical instruments, that obtained by most clinical workers. Some text-books are evidently written for those with no previous chemical knowledge or training, hence the directions for a given quantitative method are "simplified," some little steps omitted, reasons for nearly all to be taken not given, hence those little technical details the intelligent observance of which is so necessary in accurate work, are not followed, and the result must be only "clinically accurate." In proof of this let the reader compare the directions for a quantitative procedure in many text-books with those given in Neubauer and Vogel's Analyse des Harns, or other standard works on chemical analysis, and he will find the surprising thing that the more advanced the training of the workers for whom the book was written, the more minutely are the directions given.

Then, again, some instruments on the market are advertised or best described as "clinically accurate." They are made in large numbers and are not carefully standardized. The 10 ccs. mark does not mean just 10 ccs., the figure 70 per cent may indicate a color nearer 60 per cent, etc. The makers say they are "accurate enough for clinical work." True, the clinical chemist seldom wishes to know nearer than 10 per cent of the accurate amount, and accuracy of even that degree often seems an unnecessary refinement since the body in which he is interested may increase 500 per cent or more. "Is it rising or falling" is all he usually asks. Well and good. Let him understand that such results are only approximate, but that so are the results he gets by some long expensive method which is still a clinical modification of a good chemical procedure, and which he calculates to the third decimal point, thus showing his confidence in their accuracy.

If thirty separate determinations of the same substance be made independently by thirty persons or pairs of persons, the variations will be greater than one would, at first thought, expect, and yet those getting results somewhat divergent from the others (not the most so) will say with an injured tone, "I repeated the determination three, four or five times and got exactly the same result each time." To make control tests of one's own work, always essential, may show a worker how accurately he works, not how accurately he applies a given method. The inaccuracy of instruments will explain some, but by no means all of the variations in results

obtained by several instruments; but most important is the personal equation of the various workers. By this we mean the difference in skill shown in their work, and in volumetric analysis especially, the difference in idea as to what the end reaction is; and unless a worker has himself standardized the various solutions he uses, it is hard for him to know just what to call an end reaction, for in some of the analyses used in clinical chemistry the end reaction is not a sharp one, and concerning it the element of judgment is very important. In the following report only a few tables are given, and those chosen are the most characteristic, not necessarily the best. The class always had qualitative work on hand or interesting specimens to study, hence not all did their quantitative work on the same day, hence the difference in the number of determinations handed in. But in each table every result is given which was handed in, including the worst. Another point to be emphasized is that each determination recorded is the work of different students. In no case have two results by the same persons been included. We do not print these to show how accurately the work can be done—to show that one student would have been asked to make a series of control tests and the accord of his results would have surprised even himself; but to show how great variations will be found in the results of twenty to thirty independent determinations, that the reader, if he were not previously a student of chemistry, might ask himself, "where in that table would my result have stood," and since only one result of any determination can be correct, "how far are mine, which cost so much time and in which I place such confidence, how far are they from the correct one?"

In the following columns we cannot attempt to give a full discussion of a subject, the technic of a method, etc.—this can be found in any good text-book of chemistry, not clinical chemistry—but to speak of the accuracy of these methods.

BLOOD INSTRUMENTS.

1. BLOOD COUNTING. a. *Thoma-Zeiss Apparatus.*—This method is in such general use, the technic and limits of accuracy so well discussed in the several text-books of hæmatology, that here it will receive but passing notice. The satisfactory use of this instrument requires practice—one can easily see the results of even a few weeks' vacation, and will make two or three counts before his technic becomes again satisfactory. The greater the adroitness in filling the mixer and the cleaner the slide and cover-glass, the fewer the cells which need be counted. Our students are taught to count at first twice the necessary number of unit squares and only diminish that number as they find the figures of the last units do not change the average. One point not enough emphasized in text-books is that the whole blood-covered area of the ruled slide should be examined first with low power, and no matter what distribution obtains over the ruled square, if over the whole field the cells are not quite uniformly distributed, the slide should be cleaned up and another drop examined.

In leucocyte counting the students are taught to make up a fresh acetic acid solution for each day, since single yeast cells often are counted as leucocytes. They are given a bottle of glacial acetic acid and another empty bottle with a label stating how many drops of the acetic acid must be added to the bottle filled to its neck with distilled water to give the desired percentage (0.5-1 per cent). They are also taught to use the 1:10 mixer when leucocytes alone are to be counted.

b. *Oliver's Hæmocytometer.*—This ingenious little instrument has been often considered merely an easy method of getting an approximate blood count. Oliver expressly states that he intended it as a more accurate method than the Thoma-Zeiss as ordinarily used, and invented as a means of detecting slight physiological variations of normal blood which would have escaped notice in the usual method of blood counting. It was standardized by comparing it with blood counts in which very many squares were counted (120), far more than could be counted in clinical work. The author distinctly warns that the instrument is inaccurate in the anæmias and recommends that its use be limited to normal cases. But the clinician has no interest in normal cases and it seems unfortunate that such an easy method should not be used in the abnormal cases, in which alone he is interested, hence it has been used and its use recommended for such cases. In testing this instrument for normal blood, several independent observations were made by as many persons on the same case at the same time, and the blood counted for the most part by the writer. The students were in this case for the most part picked students, that the instrument might receive as fair a testing as possible.

A few of the results are given below. It should be remembered that each reading given is a separate determination—in no case are two readings of the same blood mixture given or two by the same person. Two instruments were in use.

Case.	Oliver's Hæmocytometer.	Thoma-Zeiss.	Difference.
I.	6,000,000	5,587,000	413,000
	5,900,000		313,000
II.	5,800,000	5,675,000	125,000
III.	5,650,000	5,650,000	
IV.	5,500,000	5,400,000	100,000
V.	5,750,000	5,250,000	500,000
VI.	5,500,000	5,300,000	200,000
VII.	5,650,000	5,450,000	200,000
VIII.	5,350,000	5,420,000	−70,000
IX.	5,600,000	5,616,000	−16,000
X.	5,800,000		−36,000
	5,600,000	5,836,000	−236,000
	5,200,000		−636,000
XI.	4,900,000	5,100,000	−200,000
	4,950,000		−150,000
	5,125,000		25,000
	5,050,000		−50,000

Case.	Oliver's Hæmocytometer.	Thoma-Zeiss.	Difference.
XII.	5,050,000	5,300,000	−250,000
	4,950,000		−350,000
	5,000,000		−300,000
	5,100,000		−200,000
	5,050,000		−250,000
XIII.	5,550,000	5,332,000	218,000
	5,500,000		168,000
	5,550,000		218,000
	5,500,000		168,000
	5,475,000		143,000
	5,150,000		−182,000
	5,200,000		−132,000
XIV.	4,700,000	4,916,000	316,000
XV.	5,487,500	5,228,000	259,500
	5,228,000		

It will be seen that several persons determining the same blood independently will get results which sometimes agree markedly, and that these results agree well with the actual count. But these cases were fairly normal.

As soon as we began to study the anæmias a different state of affairs was found. Sometimes the count given by the Oliver instrument was too high (in the pernicious anæmias), sometimes too low (in chlorosis and the secondary anæmias).

I. Anæmia Splenica.

Oliver's Hæmocytometer.	Thoma-Zeiss.	Difference.
3,500,000		−188,000
3,800,000	3,688,000	112,000
3,900,000		212,000
3,700,000		12,000

In this case the results were fairly satisfactory.

II. Malarial Anæmia.

2,100,000	2,800,000	.....
2,100,000	Count was made	.....
2,100,000	on following	.....
2,400,000	day.	.....

III. Chlorosis?

3,900,000	3,520,000	380,000
3,850,000		330,000
4,000,000		480,000

The diagnosis of chlorosis was made from the clinical history of the case: a young woman previously treated here for chlorosis. The entire blood picture suggested pernicious anæmia.

IV. Pernicious Anæmia.

3,900,000	1,725,000	2,175,000
3,675,000		1,950,000
2,850,000		1,125,000
2,850,000		1,125,000

V. Pernicious Anæmia. Same case as IV but some time later.

2,800,000	1,256,000	1,544,000
2,900,000		1,644,000
2,750,000		1,494,000
2,775,000		1,519,000

At this point Dr. Baumgarten began a closer study of the instrument. His results will be found in the BULLETIN of the Johns Hopkins Hospital, July, 1902, to which the reader is referred. Briefly stated, he found the errors due to the coagulation of the plasma and to difference in size of cells, so great that the instrument cannot be recommended for clinical work.

c. *The Hæmatocrit.*—We find this instrument useful in determining the presence of lipæmia, cholæmia, hæmoglobinæmia, etc, but not to count the cells.

2. HÆMOGLOBINOMETERS.—Much time was spent by the class practicing with five of the hæmoglobinometers now in general use, the v. Fleischl, Miescher, Dare, Gower, and Oliver instruments. Comparative tests with these instruments are of little use, for two questions are to be answered concerning each: Is the idea on which the instrument is based a good one? Do the instrument makers furnish a good instrument based on this idea? These two points should be clearly kept in mind. The v. Fleischl instruments are I think excellently made, yet they are fast going out of use because of the sources of error inherent in the instrument. The excellent Gower's instrument, on the other hand, has been brought into much disrepute since the market is flooded with worthless specimens. The scales of hæmoglobinometers can with difficulty be compared. One maker considers 13.88 grms. of hæmoglobin per 100 ccs. of blood normal and makes that 100 per cent, another uses a little higher amount, and some instrument makers seem to guess at it.

It is much to be desired that soon no instruments will read in percentages, but all in grams of hæmoglobin per 100 ccs. of blood. The former method is artificial and is now being abandoned. Supposing we call 13-14 grms., normal for an adult 25-45 years of age. Since a child from 6 months to 5 years of age has normally but 10-11 grms. per 100 ccs., an instrument made for children's blood must call that 100 per cent. Examine such blood with an instrument graduated on the 13-14 grm. basis, that in general use, and the reading would be 75-80 per cent; in the case of a child 5-15 years, 80 per cent; 15-25 years, 88 per cent; and 45-60 years, 87 per cent (Stierlein, Arch. f. kl. Med., XLV, 1889).[1] Yet in each case the blood is normal for that age; i. e., really 100 per cent. I remember the remark a practitioner made concerning chlorotic girls, that it was easy to get their blood to 85 per cent but very hard to raise it to 100 per cent, which would be to give it an abnormally high content of iron. If the method of expression, "grams per 100 ccs." were used, not so many patients would seem to be a little deficient in hæmoglobin, for we would be more likely to bear the age scale in mind.

a. *v. Fleischl Hæmoglobinometer.*—This formerly much-used machine is now less a favorite. Its expense, size, inconvenience in use, but especially its many sources of error (which are very well discussed in many text-books of clinical examination of the blood, Sahli, Cabot, Ewing, Da Costa), have all diminished its popularity.

b. *Miescher's Modification of v. Fleischl's Hæmoglobinometer.*—This is an excellent instrument, the sources of error in the Fleischl are practically all removed, and probably it

[1] Quoted by Sahli.

is to-day the most accurate instrument we have. But its use requires practice, good technic, and longer time than is available in the case of a practitioner, hence it will remain a laboratory instrument. It reads grams per 100 ccs.

c. *Gower's Instrument* is an excellent one when well made. Sahli recommends it above all others to the practitioner. I first learned its value in a large German clinic where the director told me they used only that, since it was certainly superior to the Fleischl. Yet the latter is a German, and the former an English instrument. It is neat, easy to use, and quite accurate. But much care must be exercised in buying it, for the emphatic language of Sahli is justified, who advises his readers to obtain their instruments from the dealers he mentions, since several manufacturers are supplying the market with instruments made in a dishonest manner and unfit for use, which, both as regards their calibration and the quality of the color solutions, would not satisfy the requirements of a person with the most modest expectations. We thought as much once, on receiving six with tubes of various shades.

d. The *Dare instrument* is a new hæmoglobinometer which promises to replace many of the others. Its ease in use and the sound principles on which it is based will perhaps give it first place among the practical instruments and perhaps among the scientific ones. One point much in its favor is the ease in reading slight differences in per cent of hæmoglobin, as is shown by the agreement in readings of two persons of one specimen of blood; or, what is more important, the quite marked agreement in readings of several persons each using a separate instrument, or at least different blood drops. The following are hæmoglobin determinations made with the Dare instrument, the determinations made independently by different persons either with different instruments or each with fresh specimens of blood of the same case at practically the same time. Those used to other instruments and who remember the difference of opinion two persons may have in reading even the same blood mixture, will appreciate these few figures.

Case.			
I.	Four instruments	in use.	—85, 85, 88, 88, 87.5, 87, 89 per cent
II.	Three	"	" 72, 71, 69, 69, 75 per cent.
III.	Two	"	" 86, 85, 87, 90 per cent.
IV.	Two	"	" 85, 85.5 per cent.
V.	Two	"	" 99, 97 per cent.

And yet the Dare instrument has its weak points. The pipette plates are evidently easy to break in using the instrument, judging from the number broken in the use of our six during the past year. The readings must be made at once before the blood coagulates, which sometimes means rapid work.

e. The *Oliver instrument* has some advantages over the Fleischl but we could find none over the Dare.

The *Talquist scale* was little used because we desire an accuracy greater than it advertises to give, and yet I dare say the experienced eye will, with this simple, cheap affair, get more accurate results than many less trained persons can with the Fleischl.

Gastric Analysis.

In all clinical chemistry there is perhaps no subject in which quantitative determinations are of greater value and are easier to make than that of gastric diseases. The apparatus is simple, the fluids few, and the time required short. What is of greater importance is, however, the fact that the results obtained are of considerable value in diagnosis, are, in fact, indispensable. The points to be determined in all cases are: (1) total acidity; (2) if free HCl be present, its amount; (3) if no free HCl be present, how much must be added before the test for free HCl can be obtained, i. e. the HCl deficit. Several other quantitative tests are valuable in certain cases. Knowing these few figures, much is known concerning the gastric juice, the nature and degree of the disease, the motility of the stomach, etc. In the following determinations one-tenth normal NaOH and HCl were used, and the results are expressed in number of cubic centimeters of these solutions used. These multiplied by 10 would give "acidity per cent," and multiplied by .0356 would give the percentage by weight of HCl, since in all cases 10 ccs. of gastric mixtures were used. The indicators used were phenolphthalein for total acidity, Congo red paper, dimethylamidoazobenzol, and Günzburg's reagent for free HCl.

In the case of *phenolphthalein* there should be very little difference of opinion concerning the end reaction. The examination of Tables I and II will show this to be the case, yet in Table III, in which every figure is the result of very careful work, there would seem to be considerable. The reason was that in the case of the first two tables the students were directed to consider the first permanent red tint the end reaction. In the case of III, those getting the higher figures informed me they had followed the advice given in very good text-books, to add the alkali till the deep red fails to increase. Hence, in so simple a test as total acidity the magnitude of the result will depend to some extent on the text-book used.

Congo red paper is an indicator for free acid, and an excellent one, not enough used, for where free HCl is present (as shown by other tests) the amount of free organic acid likely to be present will not disturb results, and yet the end reaction is one concerning which there may be considerable difference of opinion, as the table will show. For routine work it is the indicator used in as prominent a clinic as Riegel's (see Riegel, Die Erkrankungen des Magens). I imagine the wide variations in our work are due to differences in paper and the desire to be very accurate indeed, for the wet paper may look bluish.

Dimethylamidoazobenzol is an indicator for free HCl which promised well at first, but now is less used, although Hemmeter, Simon, and others, think it should replace the others, since it is "both simple and sufficiently accurate for clinical purposes." It is very easy to use, but I think it safe to say that in many clinical laboratories which make a specialty of

gastric analysis it is not used except as an approximate indicator, yet perhaps sufficiently accurate for clinical purposes. The end reaction is not sharp.

Günzburg's (phloroglucin-vanillin) reagent is the best, the most sensitive, the surest, indicating nothing but free mineral acid, i. e. free HCl. Applied in the way suggested by Sahli (adding 25-30 drops of indicator to 10 ccs. of gastric contents and warming the drop on the stirring rod after each addition of NaOH solution) it is by no means a time-consuming procedure, although it is not difficult to use the porcelain dish as usual, as the class did, and the certainty of the result renders it a most satisfactory reagent.

Examination of the annexed tables will show several facts: First, that in no case do all agree when the end reaction is reached; second, that there is greater unanimity of opinion concerning Günzburg than either of the other two; and lastly, that although it is the most delicate test, the amount of HCl indicated by it is less than by the others, and in the case of an HCl deficit, the deficit indicated by Günzburg is the greatest, showing that in the case of the artificial mixtures examined, Günzburg's reagent is less influenced by other constituents of the mixture than are the others.

Although there is some good opinion to the contrary, I think that the weight of evidence is much in favor of Günzburg's reagent as the best indicator in HCl determinations, when accuracy is desired, and that these few tables show that more constant results are obtained by its use than by the others.

The mixtures examined were solutions of Witte pepton, to which the desired amount of HCl was added.

Again, we repeat, the same student was not concerned in any two determinations. Each is the work of a pair of students, all the pairs working quite independently.

GASTRIC ANALYSIS I.

Total Acidity.—2 determinations gave 8.5 ccs. $\frac{n}{10}$ NaOH.
2 " " 8.6 "
4 " " 8.7 "
5 " " 8.8 "
6 " " 8.9 "
1 " " 9.1 "
Hence, of 20 determinations 15 gave 8.7–8.9 "
Greatest difference 9.1—8.5=0.6 ccs.

Free HCl.

a.—Congo red as indicator.
5 determinations stood between 2.9–3.9 ccs.
6 " " 4.0–4.9 "
8 " " 5.0–5.8 "
Difference of extremes 5.8—2.9=2.9 "

b.—Dimethylamidoazobenzol.
13 results stood between 4.1–4.9 ccs.
7 " " 5.0–5.4 "
Difference of extremes 5.4—4.1=1.3 "

c.—Günzburg's reagent.
15 results stood between 2.2–2.9 ccs.
3 " " 3.0–3.3 "
Difference of extremes 3.3—2.2= 1.1 "

GASTRIC ANALYSIS II.—HCl Deficit.

Total Acidity.—6 results stood between 5.1–5.5 ccs. $\frac{n}{10}$ NaOH.
8 " " 5.6–6.0 "
1 result was 6.6.
Of these 10 results stood between 5.5–5.8
Difference of extremes 6.6—5.1=1.5 ccs.

HCl Deficit.

a.—Congo red paper.
7 results stood between 0.5–1.9 ccs. $\frac{n}{10}$ HCl.
3 " " 2.0–2.9 "
6 " " 3.0–3.9 "
4 " " 4.0–4.3 "
Difference of extremes 4.3—0 5=3.8 ccs.

b.—Dimethylamidoazobenzol.
1 result was 0.6
9 results stood between 2.0–2.9
7 " " 3.0–3.9
1 result was 4.4
1 " " 5.1
Difference of extremes 5.1—0.6=4.5 ccs.

c.—Günzburg's reagent.
6 results stood between 3.6–3.9 ccs. $\frac{n}{10}$ HCl.
12 " " 4.0–4.5 "
Difference of extremes 4.5—3.6=0.9 ccs.

GASTRIC ANALYSIS III.

In the final examination in clinical microscopy and chemistry was the following question: "Determine the total acidity and the free HCl or HCl deficit, whichever the case may be, of the given fluid. Use whatever method you choose." Each student worked independently and we may be sure did each determination at least twice, since accuracy in use of any method used was the element under examination. The following is a record of the entire work done, some using but one, some all three methods for HCl.

Total Acidity.
23 determinations stood between 18.1–18.9
26 " " 19.0–19.7
Difference in extremes 19.7—18.1=1.6

As already stated, their idea of the end reaction varied, some stopping at the first red, some at the point at which the red ceases to deepen.

Free HCl.

a.—Congo red paper.
3 determinations stood between 10.0–10.9 ccs. $\frac{n}{10}$ NaOH
5 " " 11.0–11.9 "
5 " " 12.0–12.9 "
Difference between extremes 12.9—10.0=2.9 ccs.

b.—Dimethylamidoazobenzol.
2 results stood between 10.0–10.9 ccs. $\frac{n}{10}$ NaOH
7 " " 11.0–11.9 "
8 " " 12.0–12.9 "
4 " " 13.0–13.9 "
3 " " 14.0–14.3 "
Difference between extremes 14.3—10=4.3 ccs.

c.—Günzburg's reagent.

15 results stood between 9.4–9.9 ccs.
10 " " 10.0–10.5 "
1 result was 12.6 ccs.

Of these, 20 results stood between 9.7–10.2 ccs.
Difference between extremes 12.6–9.4=3.2 ccs., and excluding the one evidently wrong result, 1.1 ccs.

Should the objection be urged that the above solutions lacked many constituents and properties of real gastric contents our answer is that since this is so the errors in the analysis should be less. To test total acidity is an easy, accurate method. The amount of HCl free or deficient is not difficult to determine and if Günzburg's reagent be used, quite accurate.

URINARY ANALYSIS.

Of the many valuable quantitative tests for different constituents of the urine, the few following ones are chosen:

Uric Acid.—Many still think the determination of this acid very important, although the many charges against uric acid in the court of pathology have been withdrawn one by one till scarcely any remain. In class work and also for the practitioner the best method, the Ludwig-Salkowski, cannot be used, and of the permanganate methods the Folin modifications of the Hopkins method are the best. Folin's two modifications were used in class work. A description of the most recent (Zeit. f. phys. Chem., Vol. XXXII) can be found in Simon (Manual of Clinical Diagnosis, 4th ed.) In this method the phosphates and an unknown mucoid body are first removed by precipitation with uranium acetate, after which the uric acid is precipitated by the ammonium sulphate which was in the same solution with the uranium acetate, by adding ammonia. This method has been given a critical examination in this clinical laboratory by Dr. Baumgarten, who finds it is not all that might be desired and whose work will appear later.

In the case of the following determinations, one specimen of mixed urines was collected and the uric acid determined half by the former Folin method, half by his later method. The answer is given as grams in 1 liter.

Urine I.

Folin 1st method.

1 result was .397 gms.
4 " stood between .400–.449 gms.
4 " " " .450–.499 "
12 " " " .500–.532 "

Folin 2nd method (same urine.)

1 result was .385 gms.
3 " stood between .400–.449 gms.
12 " " " .450–.499 "
6 " " " .500–.544 "

Urine II.

Folin 1st method.

12 results stood between .523–.599
9 " " " .600–.700
Difference between extremes .700–.523=.177 gms.

Folin 2nd method (same urine.)

9 results stood between .249–.299 gms.
8 " " " .300–.344 "
Difference between extremes .344–.249=.095 gms.

The determination of uric acid by this or any method requires good reagents and good technic, and I was surprised that the results came as closely as they did. The advantage of the second method is claimed in the case of pathological urines, in which case the bodies removed by uranium acetate disturb the determination. The chief sources of error are first the reagents, for the ammonium sulphate should be chlorine free, and some of the salt sold under that name is not. The ammonium urate precipitate must be washed with 10 per cent ammonium sulphate solution till the filtrate is quite free from chlorine, or the error will be considerable; and lastly, but of most importance, the end reaction must be thoroughly understood. It is in this case no very sharp point, hence according to the directions given in one text-book the red color should remain at least 30 seconds; in another, the end reaction is the first red color throughout the whole mass of fluid; again, 5 seconds is the limit. The rule of the pure chemist to titrate to color is a hard one it would seem for the clinical chemist to follow, yet this difference in time limit of reaction may mean .03 gms. per 1 liter, in some cases perhaps more. The use of uranium acetate in the latest method of Folin does seem to make the end reaction sharper.

Chlorides.—The volumetric determination of the chlorides by means of the Volhard and Falck method is one of the most satisfactory which the clinical chemist is called upon to do, because of its accuracy. This method was practiced by the class both as recommended by Arnold (Neubauer and Vogel, Analyse des Harns), and by Lütke (Sahli, Klinische Untersuchungsmethoden). The advantage of the latter is that the silver nitrate, nitric acid, and iron alum, are all in one solution, hence the separate bottles for, and separate addition of, the two latter are dispensed with.

In the following table are the separate determinations of the chlorides in one specimen of urine, both methods being used. The answer is given in percentage of sodium chloride, i. e. grams per 100 ccs.:

Arnold method.

2 results stood between 1.26–1.29 per cent.
7 " " " 1.30–1.35 "
14 " " " 1.36–1.40 "
of these 18 " " " 1.34–1.39 "
Difference between extremes 1.39–1.26=0.13 per cent.

Lütke method.

11 results stood between 1.35–1.39 per cent.
1 result was 1.48 "

That the simpler technic of the Lütke procedure was an advantage might be concluded from the less variation in those results, yet the number of determinations made was fewer.

Phosphates.—The volumetric determination of phosphoric

acid is another determination in which the clinical chemist finds pleasure and satisfaction.

The method used is described best in Neubauer and Vogel, i. e. to 50 ccs. of urine are added 5 ccs. of a solution of sodium acetate 100 gms., glacial acetic acid, 30 grms. in 1 liter of water. The urine was then kept at boiling point and the standard solution of uranium nitrate added till the end reaction is reached.

Two indicators were used, cochineal, a very pretty indicator and much the easier to use, and potassium ferrocyanide, the indicator more generally used and perhaps with fewer objections. One thing must be borne in mind: these indicators do not indicate the same reaction, and that one must be used which was employed to standardize the uranium nitrate solution, or gross error will arise. In the following table one urine was studied, both indicators used, and but one uranium solution which had been standardized with cochineal as indicator. The amounts given are grams of P_2O_5 in 1 liter of urine.

Urine I.

Cochineal as indicator.

3 results stood between 1.65–1.69 gms.
33 " " " 1.70–1.77 "
of these 18 " " " 1.72–1.73 "
Difference between extremes 1.73—1.65=.08 gms.

Urine II.

Potassium ferrocyanide as indicator.

10 results stood between 1.82–1.89 gms.
9 " " " 1.90–1.99 "
5 " " " 2.00–2.08 "
Difference between extremes 2.08—1.82=.26 gms.

Cochineal as indicator.

5 results stood between 1.73–1.79 gms.
18 " " " 1.80–1.85 "
2 " " " 1.87–1.94 "
Difference between extremes 1.94—1.73=0.21 gms.

This latter was the Class's first attempt at this determination. The difference in the indicators is well seen. The cochineal is not only easier to use but the students agreed much better in their results. That these two indicators do not show the same end reaction, is well shown. Yet the success of cochineal as a good indicator in urinary examination must not lead one to conclude that this method can be used to determine phosphoric acid in other fluids.

Sugar.—In the case of some necessary determinations the practitioner is satisfied with approximate results, some determinations being made because of their scientific interest rather than practical importance; but the determination of sugar in the urine is of great importance to the patient, and unless done accurately it has little or no value. The physician will govern the treatment and diet of a case according to the difference in amount of sugar after certain experiments with the diet; but what is of greater importance, although probably still out of the reach of the practitioner, the difference between the amount of sugar as shown by titration and that by the polariscope is an excellent method, perhaps the best, of judging the amount of oxybutyric acid in the urine; and the need of accurate determination of the degree of acidosis must become clearer and clearer as the importance of the condition is better understood.

Unfortunately the titration of sugar by means of Fehling's solution is not easy, but requires considerable training and is perhaps the hardest determination to do well that the clinical chemist will make. Also it is a rather long process, at least one-half an hour being necessary.

Several modifications of Fehling's method have been proposed, which seem to simplify matters so far as time is concerned. These may be convenient for a person to use who is skilled in the old method, but do not seem intended for the beginner. Here, we believe in training the student in the Fehling method, and when he understands that thoroughly and can apply it accurately, he may safely attempt some shorter method, but one in which the chance for error is perhaps greater.

Accuracy in this method means attention to details, a proper dilution of the urine, and, strange it should need such emphasis, thorough mixture of the urine with the water used to dilute it; the proper arrangement of the apparatus that work may be rapid and not too hot; the proper position of the flask after adding the urine and boiling, that the "clear line" below the meniscus may be well seen (this means a white, light background); and lastly, the practice necessary to find this line and adjudge its color.

This determination is so important that the class practiced it considerably. The result of the determinations made of one urine are given.

3 results stood between 4.42–4.49 per cent. glucose.
16 " " " 4.50–4.59 " "
5 " " " 4.60–4.69 " "
5 " " " 4.70–4.76 " "
2 " " " 4.80–4.81 " "
Difference between extremes 4.81—4.42=0.39 per cent.

These figures will show that with attention to detail and some practice, the determinations are very satisfactory indeed.

Albumin.—The accurate determination of albumin is much desired by the practitioner, and with good reason, yet it would seem that this is as much out of his reach now as formerly. Even the clinical chemist finds it hard to do well, for the only good way is to coagulate the albumin so thoroughly that the filtrate gives no test, dry in a thermostat the precipitate on a weighed paper and then weigh both together. This seems simple, but it requires a thermostat, an accurate analytical balance, and much time, for the person when he begins to make the determination does not know whether the coagulation alone will consume five minutes or one hour, so difficult it sometimes is to get just the right acidity. Many approximate methods have been proposed and used: the Esbach albuminometer, the centrifuge, the determination of specific gravity or nitrogen before and after removing the albumin, refraction, polarization and various optical methods, et al., while others prefer to esti-

mate from the appearance of the nitric acid coagulum (see Ogden, Clinical Examination of the Urine).

Esbach's Albuminometer is an instrument in quite general use. It is one which, if used according to certain directions (all of which do not accompany it), would give fair results, but in the way it is used gives for the most part results which cannot satisfy a person desiring even merely approximate ones. Some of these points important in its use are that the specific gravity of the urine should by dilution be between 1006 and 1008; that the amount of albumin should (by dilution) be not above 4 per m. (0. 4 per cent); but what is of prime importance, the temperature of the room in which the tube stands for twenty-four hours should vary little from 15° C. This last is a requirement which the practitioner cannot fulfill, and yet its importance is the greatest. Christensen (Virchow's Arch., Bd. 115, 1889) found that in some urines a difference in temperature of 5° C. could cause a difference in readings of 100 per cent. If such an error is possible the instrument is almost useless as a quantitative instrument. We have used the instrument considerably and give a few illustrations of the results as compared with results obtained gravimetrically, and those with the Purdy centrifuge. In a building in which the temperature in some rooms remains fairly constant, the instrument may be of good service, but unless this is the case it could hardly be relied upon to determine whether albumin was rising or falling. One can, of course, by means of it tell whether albumin is less than 1 per m. or between 1 and 3, 3 and 5, 5 and 7 per m., etc., but that errors are considerable is well seen by consulting the above-mentioned article of Christensen. The results we give are a very few examples of a long series of parallel determinations. So many such trials of the instrument have been published and since scarcely one text-book of clinical chemistry gives the instrument more than faint praise, more tables are not necessary. These parallel tests were made, not under the conditions at which the instrument would give its best results, but purposely under those conditions under which the practitioner is forced to use it. Hence the urine is in all cases acidified and diluted, but not placed in a room of constant temperature, although the temperature did not vary much.

The *Centrifuge Method* has been resorted to for many determinations, and among these of albumin. The method is variously applied, but perhaps best by Purdy, whose latest modification is found in the fifth edition of his book. He lays great stress on the necessity of diluting the urine till the percentage of albumin shall be less than 0.2 per cent by weight; (10 vol. per cent) on the length of the arm of the centrifuge, and on the speed used. When one considers the effect which a difference of half an inch in radius of rotation of the column of urine, and the influence which the change of a few hundred revolutions per minute have on the force which packs the precipitate into the point of the tube, he can easily see the need of following Purdy's directions to the letter if he wishes to use this author's tables for calculating his results. I determined to follow all these directions carefully. Purdy's centrifuges are in great variety on the market and finely graduated tubes are in as many various lengths (they are graduated for volume, and this was accurately done in all I tested). To fulfill Purdy's specifications a new centrifuge arm had to be made to order, that the distance from the center of rotation to the tip of the tube should be just 6¾ inches. A good speed indicator was used at each determination that a speed of just about 1500 revolutions could be depended upon. This is an important point, since the electric current did vary at different times of the day, and a difference in speed in either direction is important. The instrument was stopped just at three minutes, and the reading made. Under these conditions the precipitate is by no means of the minimum volume, but only under these conditions could Purdy's tables of relation between volume and weight per cent be used.

The figures in the following table are all "weight per cent" (i. e., 0.2598 per cent = 2.598 per m.).

	Gravimetric.	Esbach.	Centrifuge.
I.	0.2908	0.28	0.229
	0.2984	....	0.292
II.	1.1592	0.68	1.252
	1.1454	....	1.416
III.	0.7280	0.43	0.688
	0.7260	....	0.646
IV.	0.2884	0.2	0.292
	0.2834	....	0.271
V.	0.4900	0.27	0.390
	0.4806	....	0.422
VI.	0.3458	0.49	....
	0.3489	....	....
VII.	0.2055	0.17	....
VIII.	0.3314	0.26	....
IX.	0.5624	0.18	0.354
	.....	....	0.374
X.	0.2836	0.26	0.250
	0.2848	....	0.292
XI.	0.3030	0.15	....
	0.3096	....	...
XII.	0.8976	0.50	....
	0.8824	....	....
XIII.	0.3128	0.2	....
XIV.	0.6148	0.3	....
	0.6066	....	....
XV.	0.6194	0.4	....
	0.6124	....	....

From these figures it will be seen that neither of these methods is a very satisfactory way of estimating albumin. Accurate results are sometimes obtained, often with the centrifuge, but not so labelled that they may be recognized.

Urea by the Doremus Tube.—This little piece of apparatus is so much used and the advantages, especially of its various modifications, so well recognized that a few words on its use may not be out of place. Our medical students practice with the simple Doremus tube, although the Hinds' modification is much better. But we shall not speak of the students' use of the method, but of the nurses', for we hope the time is not far distant when the urea chart will be the duty of the trained nurse as well as the temperature chart; for the suc-

cessful use of the urea tube depends on skillful manipulation rather than scientific training, and a nurse can be trained to make the determination as satisfactorily as can the doctor.

The Intermediate Class of the Nurses Training School connected with the Johns Hopkins Hospital is given a course in urinary analysis, consisting of lectures and laboratory work. They meet on six days, one hour a day, and are trained to make the following tests: Specific gravity; the presence of albumin (heat and Heller's tests), its amount as measured by the Esbach tube; the presence of sugar (Fehling's test) and the determination of urea with the Doremus tube. After this course they have a practical examination, testing various urines.

The following are the results of the urea determinations made at this year's final examination. The question was: "How many grains of urea per 1 l.?"

11	students	obtained	the	same	result	as	the	instructor.
8	"	"		results	1	grams	lower	than instructor.
2	"	"		"	2	"	"	"
3	"	"		"	1	" higher	"	"

Had we been able to provide them with the Hinds' modification I imagine their results would have been even more uniform, yet those who have used the apparatus with its 1 cc. pipette cannot fail to appreciate the uniformity of the above figures. I would also add that not one of the twenty-four nurses was in error concerning the presence or absence of sugar and albumin.

Again we wish to repeat; these reports of class work are given not as models of accuracy—we certainly would not claim that—but in hopes that some of the many interested in clinical chemistry, yet who have not had the advantage of good training in pure chemistry, may have a clearer idea of what accuracy they may expect to attain should they wish to use any of the above methods. Our advice to such a person would be to work in clinical chemistry as much as he is able, for he will be more than amply repaid thereby, but to waste no time with a questionable method; and having first chosen a line of work, practice his method on artificial solutions of known composition, then by controlling his work by parallel determinations, not made under exactly the same conditions, be sure his method has been rightly applied to the fluid in question.

ALBUMINOUS EXPECTORATION FOLLOWING THORACENTESIS, WITH REPORT OF A CASE.

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(*From the Clinic of Professor Osler.*)

Albuminous or serous expectoration following thoracentesis is one of the rarest events in pleural effusion. The first author to mention the subject was Pinault, who in 1853 reported two cases. In 1873 Terillon [1] collected twenty-one cases. Following the appearance of his monograph the subject received for nearly two years a very animated discussion in the French journals and several additional observations were reported. West [2] in 1896 estimated that the total number of recorded cases was probably under fifty; while Ortner [3] in 1899 thought that the total number of cases in the literature at the greatest was only about thirty. This latter figure is probably too low an estimate.

Ewald [4] states the phenomenon to have occurred in his practice in one out of twenty-six; Martineau in one out of fifty cases of thoracentesis, but these figures give an erroneous idea of its frequency. West has seen but one instance out of a very large number of cases and his experience agrees with that of other clinicians of large experience.

Among the records of The Johns Hopkins Hospital I have been able to find but one instance of the affection.

M. J. L., æt. 25, admitted to Professor Osler's ward May 15, 1901, complaining of pain in his stomach.

Family history was good; no tuberculous history.

Personal History.—The patient had always been very healthy. He had had none of the ordinary diseases of childhood except measles. He remembered no other acute illness. He denied venereal contagion; indulged only moderately in alcohol. Six weeks previous to admission he had an attack of sharp pain under the lower border of the ribs on the left side; this he thought had been caused by straining. He was easily relieved by internal medication.

Present Illness.—Nine days previous to admission he became overheated while on a long bicycle ride. In the evening he was seized with a sharp sticking pain under the lower left ribs; this was much exaggerated on taking a deep breath; it was relieved by pressure. There was no chill; patient does not think he had fever. He was able to continue at his work but felt badly, lost his appetite and complained of some shortness of breath. He occasionally had a slight cough but no expectoration.

Physical examination on admission showed a well-nourished, healthy looking man; mucous membranes of good

[1] Terillon, De l'expectoration albumineuse après la thoracentese, Paris, 1873.

[2] West, Transactions of the Clinical Society of London, 1896, vol. xxix, p. 169.

[3] Ortner, Wiener klinische Wochenschrift, 1899, p. 1090.

[4] Ewald, Cf. ref. in Wilson Fox—Diseases of Lungs and Pleura, p. 1070.

color; the tongue clean. The patient was not suffering from dyspnœa; the respirations were thirty-two to the minute. The pulse was one hundred; of rather small volume and low tension.

Examination of the thorax revealed slight prominence of the left upper front with obliteration of the interspaces in the left axillary region. The expansion of the entire left side was diminished. Tactile fremitus was absent throughout the lower left axillary and subscapular regions. The percussion note was impaired and of Skodaic quality in the first left interspace. In erect posture flatness began at the level of the second rib; in recumbent posture at the level of the second interspace. The percussion note was flat throughout the axillary region and over the entire left back as high as the level of the spine of the scapula. On auscultation a few moist râles were heard over the left clavicle and the left supraspinous fossa. Over the area of flatness the breath sounds were very distant.

The right lung was practically negative; a few moist râles were heard at the extreme base.

Heart.—Cardiac impulse was seen in the third and fourth right interspaces almost to the nipple line. Relative dulness extended to a point eight centimeters from the median line in the fourth right interspace; absolute dulness to a point five centimeters from the median line in the same interspace. The heart sounds were clear.

The remainder of the physical examination was negative.

Owing to the extent of the effusion it was deemed best to aspirate and accordingly, on May 16, a needle was inserted in the eighth interspace in the posterior axillary line. After 320 cc. of turbid, yellow fluid had been withdrawn the flow suddenly ceased and no more fluid could be obtained from that situation. The patient experienced no unpleasant after effects.

On May 20 a needle was again inserted in the left side posteriorly but after withdrawing 730 cc. of turbid fluid the aspirating apparatus began to leak and the tapping had to be abandoned. Again the patient experienced no unpleasant symptoms.

On May 23 a third attempt was made and this time 3100 cc. of fluid were withdrawn. The aspiration was done slowly and three interruptions were necessary in order to change receiving bottles. Towards the close of the operation the patient began to complain of slight shortness of breath and of a smothering sensation. After about half an hour there began a series of severe paroxysms of coughing, each being followed by profuse expectoration of serous, frothy sputum. The paroxysms followed each other at very short intervals and the patient complained much of dyspnœa. After lasting about one hour the symptoms gradually subsided but the patent continued to expectorate for two or three hours longer.

The total amount of expectoration was not accurately measured but approximated one liter. It was very frothy, of a pale green color, translucent, and on standing deposited a muddy sediment. Treated with nitric acid it gave an abundant precipitate of albumin. Examined microscopically it contained large numbers of bacteria; many flat epithelial cells; a few red blood-corpuscles and some polynuclear leucocytes.

A differential count of the leucocytes in the effusion showed: polymorphonuclear leucocytes, 1.7 per cent; large mononuclear leucocytes, 1.9 per cent; small mononuclear leucocytes, 96.4 per cent. No tubercle bacilli could be found in a centrifugalized specimen.

The subsequent history of the patient was satisfactory; the effusion did not reaccumulate and he was discharged June 12, 1901.

Terillon divides the cases of albuminous expectoration into three classes:

I. *Mild Form.*—The expectoration may come on immediately at the close of the thoracentesis; usually a short interval elapses. The patient after being rendered more comfortable by the removal of the effusion, commences to cough and to complain of some shortness of breath and soon to expectorate a considerable quantity of clear, frothy fluid. It is expectorated at times without intermission and accompanied by almost constant cough. After lasting for a variable length of time, the symptoms gradually subside. In this form the general condition of the patient is always good and never excites alarm. The quantity of the expectoration varies from a few grams to 800 grams.

II. *Severe Form.*—This differs from the preceding in the intensity of the dyspnœa, the abundance and persistence of the expectoration and the severity of the cough. The onset is usually abrupt and the sense of oppression extreme. The symptoms rapidly reach their maximum intensity. The dyspnœa may be excessive and accompanied by a sensation of great anxiety. The patient shows signs of collapse and asphyxia; the face becomes cyanotic and the skin is covered with a cold, clammy perspiration. The symptoms may last several hours or an entire day but with varying intensity. The quantity of expectoration in this form varies between 1200 and 1500 grams.

III. *Grave Form.*—In this form the onset is sudden; the patient is suddenly seized with extreme dyspnœa and expectorates a large amount of frothy fluid; the symptoms grow rapidly worse, fluid gushes from the mouth and nose and the patient quickly dies of suffocation. In this form death may be very rapid, in some cases in less than fifteen minutes after the onset. Sometimes in fact the gravity of the accident is such that there is no time for the expectoration to appear. The patient succumbs to asphyxia and post-mortem the lung is found œdematous and the bronchi filled with fluid.

In all three forms the character of the expectoration is the same. The fluid is frothy; more or less viscid; of a slightly yellowish or greenish color. On standing it separates into three layers; the upper frothy and clear or slightly yellow in color; the middle clear or slightly cloudy according as the expectoration is abundant or small in amount; the lower denser and forming a granular deposit containing cellular elements. Occasionally slight traces of blood are

present. Tested with heat and with nitric acid the fluid yields an abundant precipitate of albumin. Acetic acid precipitates a varying quantity of mucin. Microscopical examination reveals large numbers of bacteria; cellular elements from the respiratory mucous membranes; some polynuclear leucocytes and occasionally red blood cells.

Onset.—Occasionally the expectoration begins before the tapping is completed or immediately after it. More commonly, however, an interval varying from five minutes to one or two hours elapses before the symptoms set in. Pepper[5] states that in the only case observed by him the interval was eighteen hours. In the majority of cases it is less than one hour.

Duration.—This is variable. The attack may last only a few minutes; more commonly an hour or two; occasionally as long as one or even two days. In general the duration varies directly with the quantity of expectoration, but in a case of short duration the sputum may be very abundant.

The quantity of fluid expectorated is extremely variable; usually from 200 to 700 grams; sometimes as much as two liters.

Auscultation of the lung on the affected side reveals everywhere loud bubbling râles with fine crackles at the base; signs of an œdema of the lung. Râles may also be present on the unaffected side.

Serous expectoration is not necessarily associated with the use of suction in the removal of the effusion, for it has occurred in a number of instances where the fluid was removed by siphonage. In fact, it is stated to occur occasionally in pleural effusion before paracentesis has been performed.

In a few instances albuminous expectoration has followed several tappings on the same patient. Behier records a case in which this happened four times and on both sides of the thorax. Gee[6] reports a case in which it occurred three times in the same patient.

It is an interesting and instructive fact that in most of the cases of albuminous expectoration the amount of fluid removed from the pleural cavity has been large; a liter and a half or over; in three instances as much as five liters. In our own case it was three liters. Rapid withdrawal of the fluid seems also to increase the risk of albuminous expectoration. These facts have led several authors to recommend slow withdrawal of relatively small amounts of effusion; not more than 1200 cc. at one time and not to attempt to drain the pleural cavity at one sitting.

The number of fatal cases of albuminous expectoration is comparatively large; at least a dozen have been recorded. The general post-mortem appearances of the lungs are those of extreme œdema. The albuminous fluid may also be found filling all the bronchi, the trachea, the larynx, the pharynx and even the nasal fossæ. In a number of the fatal cases adherent pericardium has been found. Scriba[7] and Ortner each record a case in which in addition to the other findings a fibrinous plug was present in the bronchi of the affected lung.

Four main theories have been advanced to explain the phenomenon of albuminous expectoration:

1. Perforation of the lung by the trocar.
2. Spontaneous perforation of the lung.
3. Reabsorption of the fluid remaining after thoracentesis.
4. Acute œdema of the lung.

1. Perforation of the lung by the trocar and discharge of the pleural fluid through the lung. The supporters of this theory lay especial stress on the similarity between the expectoration and the pleural fluid. But though having considerable resemblance to one another, in many cases they are quite different; the pleural fluid is often hemorrhagic while it is the exception for blood to occur in the expectoration. Prodhomme[8] relates a case in which 2000 cc. of pus were aspirated from the pleural cavity followed by characteristic albuminous expectoration. Other objections to this theory are that (a) no perforation of the lung has ever been found post-mortem; (b) the danger of wounding the lung in tapping a large effusion is practically nil; (c) finally, if due to a perforation, the expectoration should begin at once and not, as is usually the case, after an interval.

2. Spontaneous perforation of the lung. Although spontaneous perforation of the lung in serous effusion does occasionally occur it is an exceedingly rare event; much less common than in empyema. If the fluid escaped through a perforation, pneumothorax should result and all are agreed that this is very unusual. Finally the quantity of expectorated fluid is often much larger than can be accounted for by this theory.

3. Reabsorption of the fluid remaining after thoracentesis and its discharge through the pulmonary vesicles and bronchi. The chief argument against this view is that it is contrary to the teachings of physiology. The natural pathway for the absorbed fluid would be into the lymphatics and thence into the general circulation, and however rapid this process might be it would not be accompanied by exudation into the bronchi. Furthermore in pleurisy with thickening of the membranes the absorptive power is greatly reduced.

4. Acute œdema of the lung. This is the view that was advanced by Pinault in 1853, who described the first cases, and is the one that is accepted to-day by most observers. The physical signs observed during life as well as the post-mortem findings support it. The exact mechanism by which the œdema is produced is still an unsettled matter. Johnson[9] thinks that while the lung is compressed by the effusion and its circulation is sluggish, coagula form in the minute vessels, especially the veins. As the effusion is removed the amount of blood flowing to the lung is increased,

[5] Pepper, Philadelphia Medical Times, 1873–74, vol. iv, p. 718.

[6] Gee, St. Bartholomew's Hospital Reports, London, 1886, vol. xxii, p. 99.

[7] Scriba, Deutsches Archiv für klinische Medicin, vol. xxxvi, 1884-5, p. 328.

[8] Prodhomme, De l'expectoration albumineuse, Paris, 1874.

[9] Johnson, British Medical Journal, 1873, vol. ii, p. 479.

but owing to the obstruction offered by the coagula in the veins there results a passive engorgement of the capillaries and a consequent transudation of serous fluid into the air cells.

Duffin [10] disagrees with Johnson and thinks the œdema is to be explained by the temporary damage done to the vasomotor nerves by compression; when this is removed the vessels dilate and remain so until the nerves recover sufficiently to cause contraction of the vessels.

Cohnheim has shown that the permeability of the vessels in a lung which has been for some time compressed is considerably greater than that of a healthy lung. Most observers would explain the œdema by reason of this abnormal permeability and the rapid engorgement of the lung which follows the withdrawal of the pleural effusion.

But though this seems reasonable it yet remains to be explained why albuminous expectoration does not follow every thoracentesis inasmuch as these favorable conditions are present in every case.

Probably the explanation is to be sought in the abnormal pathological conditions which are so commonly found in the fatal cases, such as cardiac insufficiency; adherent pericardium; clots in the pulmonary vessels, etc. Ortner, in a study of twelve fatal cases, finds in at least eleven the common factor of difficult mobility or complete immobility of the mediastinum, the result of adhesions to the lungs, the sternum or the pericardium. He concludes that the œdema has for its immediate cause an abnormal permeability of the blood vessels of the compressed lung, aided frequently by cardiac insufficiency. The sudden emptying of the pulmonary vessels causes increased flow of blood to the left heart; this is unprepared for the extra exertion and there results a disproportion in work between the right and left heart and consequently lung œdema. This œdema is the more easily produced when, owing to adhesions, the mediastinum is prevented from assuming its normal position as the effusion is drawn off.

The exact mechanism by which the lung œdema is produced must still be left an unsettled question. West hints that a careful study of the lymphatics in these cases might aid in a solution of the problem.

NOTE.—Since this article was written two cases of albuminous expectoration following thoracentesis have been reported from this country. The first by Riesman appeared in The American Journal of the Medical Sciences for April, 1902, p. 620. A full bibliography accompanies the article. The second by Patek appeared in American Medicine for August 23, 1902, p. 287. Subsequent reports may show that this phenomenon is possibly not as uncommon as is generally supposed.

[10] Duffin, British Medical Journal, 1874, vol. i, p. 372.

A STUDY OF THE RETICULAR SUPPORTING NETWORK IN MALIGNANT NEOPLASMS.

AS STAINED BY MALLORY'S METHOD.

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(*From the J. H. R. Molson Laboratory of Pathology, McGill University.*)

Observations on the presence of several varieties of connective tissue in tumors have been recorded in well-known papers. Comparisons have been drawn between the distribution of the connective tissue in the sarcomata and carcinomata, but I believe that heretofore there has been no thorough comparative study of the finer supporting organization of all the types of malignant tumors—by which I mean, carcinomata, sarcomata and endotheliomata, which last type includes the peritheliomata.[1]

That such a study would be generally interesting was a foregone conclusion, but there was a possibility that it might be very useful in assisting to make diagnoses of the more obscure growths by a fairly rapid method and also establish the relations between the various types of new growths.

Mallory's method was chosen because fresh tissue is not always to be had and because I had found that the use of digestion methods was unsatisfactory in fixed specimens. This method is, beside, a particularly brilliant method of staining, for, not only the supporting tissues, but, in well-fixed specimens, the cells are clearly and brightly stained, allowing a more careful study of the relation of framework and cellular elements.

In using the method I have made a slight modification which I think brings out the colors somewhat better than the original method. This deviation is simply in the use of a drop of aniline oil on the section just after the alcohol, but the method I will give in detail.

Sections are cut from tissue hardened in Zenker's fluid and imbedded, preferably, in paraffin. These are fixed on slides in the usual way and then the paraffin is dissolved off and the slide immersed in absolute alcohol, 95 per cent alcohol, 70 per cent alcohol, then in water. They are then stained in a 1/10th per cent aqueous acid fuchsin solution for from 2-3 minutes, then washed in water; a few drops of a 1 per cent solution of phospho-molybdic acid is then dropped on the section and allowed to remain for about 5-7 minutes. The slides are now carefully washed in water and

[1] On the subject of endotheliomata and their intercellular substances I can find but a few isolated remarks, such as the one quoted from Johnston, and the one quoted from Israel's paper (Berl. klin. Woch., 1900) by Lubarsch and Ostertag (Ergebnisse, 1901), in which it is stated that endotheliomata do not lose their ability to form an intercellular substance under all circumstances, a morphological characteristic which differentiates them from the epithelial tumors.

the stain composed of aniline-blue 0.5 grams, orange G, 0.2 grams and oxalic acid 2 grams, with 100 cc. of water, is dropped on, to remain for about twenty minutes. The slides are then rinsed in water, hurriedly dehydrated with 95 per cent alcohol and then a drop or two of aniline oil is allowed to remain on until the sections are clear, when it is removed by blotting and the sections are then cleared in xylol and mounted in balsam.

By this method the finest reticular processes can be seen clearly and distinctly, and their relation to the cells studied with any power of the microscope.

Before speaking of the structure of the tumors I think it will be well to recount the structure of the tissues in which the growths arise. In doing this I can let the paper of Dr. Adami on classification speak for me, in part, for in this communication the author reviews the genesis and structure of the body layers in an extremely clear manner.

Briefly then—At an early stage of the life of the embryo there are three layers of cells developed from the one original layer; these are, epiderm, hypoderm, and mesoderm. But at a somewhat later time the mesoderm "from being a simple undifferentiated cell mass, which we may compare with the morula, certain of its cells growing outwards between the epiblast and hypoblast, become arranged into a definite layer to form or enclose the primitive body cavity. From this point onwards we can distinguish two structures of mesoblastic origin—the mesothelium, or lining-membrane portion of the mesoblast; and the mesenchyme or the mesoblastic pulp." So, as Adami says, "during embryonic life one obtains a series of differentiations of the primitive cell layers leading to the production of two sets of tissues; one which we may term the *lining-membrane tissues*, the other, the pulp tissues" (p. 5). Both of these layers become developed widely, and highly differentiated, into organs and tissues, but "even in cases where there is the widest divergence from the original type of lining membrane, we find that this distinction still holds, that the parenchymatous cells form *layers or groups of cells into which the vessels do not penetrate, and in which there is an absence of stroma between the members of the cell groups.* While, contrariwise, regarding tissues originating from the embryonic pulp, we notice that in them the prominent characteristic is that there is an *intercellular ground substance, either homogeneous or fibrillated, separating the specific cells of the tissues*" (p. 6).

It is because of such features as these that Adami speaks of tumors arising from the lining membranes of the body as lepidomata (lining membrane tumors) and hylomata (pulp tissue tumors).

The object of this paper will be to show how closely the tumors adhere to the types of tissue in which they originate —judged by the arrangement and distribution of their intercellular substance.

First of all—if, "after the embryonic period hylic tissues never take on lepidic characters," we would expect to find among the tumors that none of those arising in connective tissue of any kind would present any of the features of a carcinoma.

Second, we might expect the reverse to be true if we confine ourselves to tumors arising in mature epithelium or hypothelium.

Judging from the case reports of several writers we cannot expect the tumors arising in mesothelial tissues to possess such stable characters, and since the endothelium is a later development from a relatively undifferentiated tissue, we should expect this lining membrane to show no more permanent characters than those of the physiologically functional cells derived from mesothelium, and too, less stability than has the older hypoderm or epiderm. In view of such peculiarities of the tumors arising in these differentiated mesodermic tissues, Adami calls them the "transitional lepidomata."

When we come to study the finer supporting tissues of the class of tumors which are more usefully—for the present purpose—called lepidomata, since this term excludes those growths which may originate in other than the true covering

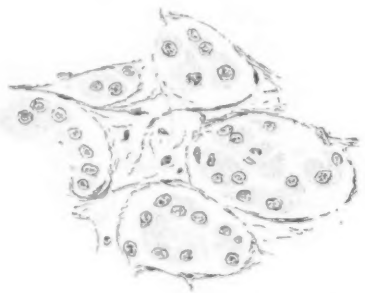

Fig. 1. Cancer of rectum. Metastasis in lymph gland. Mallory's stain. Leitz, I–6.

membranes, we are able to state definitely that the rule is for the absence of an intercellular fibrous tissue. This point White has made after a careful study of tumors, treating them by Mall's, Spaltcholz', Van Gieson's, Weigert's and Mallory's methods. The text of his conclusion is as follows: "Carcinomata possess a stroma of white fibrous tissue outlining the cell spaces, but have no intercellular network" (p. 220).

Petersen (Verh. d. deutsch. path. Gesell., 3 Tag., 1901, 61) has offered the same conclusions.

In order to be convinced and see for myself that this is true I have made Mallory preparations from a number of carcinomata of rectum, gall duct, stomach, metastases in lymph glands and adrenal, and in other organs, and have been able to reach the same conclusions, with the slight apparent variation due to the observation that in a rapidly infiltrating cancer, for instance of the stomach, when single cells are more or less isolated at the margin of the growth, the appearance may lead one to think that there is an intercellular reticulum. But if even the smaller aggregations of cells are studied it will be found that in no case is there a definite intercellular supporting network (Figs. 1 and 2).

About the cell groups in carcinomata the fibrous tissue forms a perfectly definite boundary zone with no tendency for the fibrils to branch into the cell groups.

When we come to study the sarcomata (hylomata) in the same way, we see that in rapidly growing nodules, while the reticulum is not always invariably present in the centers, that the surrounding fibrous tissue is not well defined and definite and that fibrils are dipping down into the cell masses, and that between the cells in various parts of the nodules short intercellular fibers can be seen. In gradually growing nodules the intercellular tissue will be seen complete, justifying completely White's conclusion that "Sarcomata present a larger increase in the connective tissue and possess an exceedingly fine intercellular reticular network, very similar in structure to the reticulum present in normal glandular tissue."

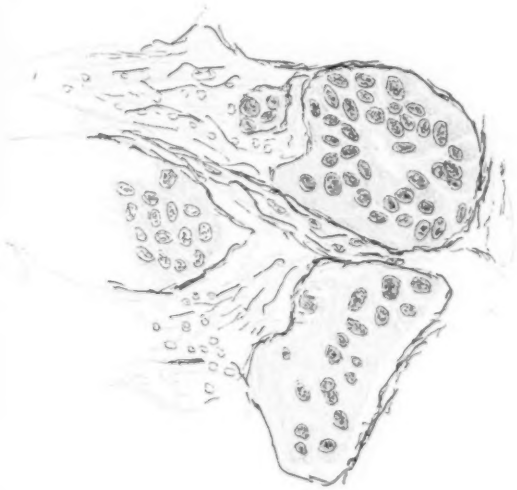

FIG. 2. Cancer of breast. Metastasis in lymph gland. Mallory's stain. Leitz, I–6.

Johnston also makes definite statements as follows: that there is a "reticulum present to a greater or less degree in every sarcoma," and that "the reticulum is entirely absent between the cells of carcinoma and endothelioma, a valuable differential point." The last part of this conclusion we will discuss presently.

Polak comes to the same conclusion with reference to the sarcomata.

I have been able to justify these conclusions after a study of several sarcoma, of stomach and mediastinal glands.

Now when we come to examine the structure of the endotheliomata (secondary or transitional lepidomata), we have to deal with a group of tumors that arise from cells differentiated from the middle germinal layer and from the mesothelium. Consequently they are embryo-genetically more closely related to the sarcomata than to the carcinomata (using the terms in their morphological sense). But with this origin and relationship they bear, nevertheless, in a great many instances, a very close morphological resemblance to the carcinomata.

As they are usually described, they form two more or less well-marked types, according to their origin in the lining endothelium of blood vessels, or in that surrounding the blood vessels, which is generally supposed to be the endothelium lining the perivascular lymph spaces.

For my study I have had a very large number of excellent specimens, about forty in all, and for the majority of these I am greatly indebted to Dr. Hektoen of the University of Chicago, and to Dr. Henry Christian of the Boston City Hospital. My method of preparing sections I have described.

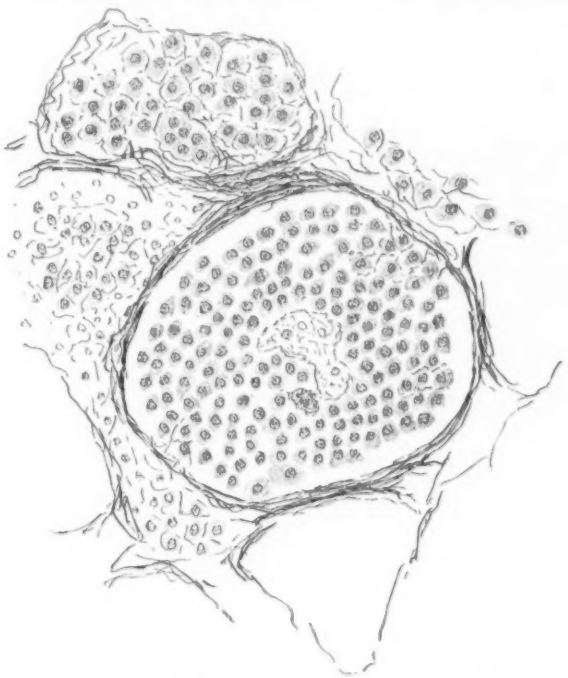

FIG. 3. Endothelioma. Mallory's stain. Leitz, I–6.

So far I have been able to find no general difference in the distribution of the reticular meshwork in the endotheliomata and peritheliomata. The only difference occurs in the very cellular, well circumscribed, and the infiltrating forms.

When the cells of the tumor growths are arranged in groups, more or less as in the carcinoma simplex, the general rule has been that these cell masses are surrounded by a well-marked fibrous tissue and with very rare intercellular fibers, but there is this difference from carcinomata, that *there is a tendency to the formation of an intercellular reticulum* which is, in some cases, only shown by filaments from the enveloping fibrous tissue dipping down into the cell masses, and in many cases branching and surrounding a few of the peripheral cells. In sections of the same tumors in which this is seen there may also be groups of cells in which the process has gone farther, and *between the majority of the cells in the group there is a definite intercellular meshwork.* This

is apparently regardless of the endovascular or perivascular origin of the growth (Fig. 3).

We see here very plainly evidence of the relationship between the endotheliomata and the sarcomata. This similarity is still more markedly shown in the infiltrating growths in which, while about the vessels the reticulum is scarce, the cells are separated by a well-marked reticulum and has all the appearance of a sarcoma.

I am convinced that this appearance is not due to the presence of the reticulum of the normal tissue into which the cells have penetrated, because the arrangement is too definite and general, and is entirely unlike the picture presented by the infiltrating carcinomata, when a few cells may be seen surrounded by the blue-stained fibrils. In cancers there are few examples in a specimen of a regular intercellular formation, and these few examples would be no more than we might expect, simply as an artefact, due to the cutting through the end of column of cells, the whole surrounded by a reticulum.

The conclusions that I have drawn are that the alveolar endotheliomata show, at the least, a partially-formed intercellular reticular network; at the most, an almost complete one; and that the infiltrating forms show a complete meshwork which corresponds to that of the sarcomata; that all endotheliomata of whatever origin show a tendency to a sarcomatous structure as regards the relation between cells and reticulum.

The application of this, in at least one way, is obvious. It represents most graphically the peculiarities of the derivation of the middle germ layer in its instability compared with the cells of the other layers, and brings out quite prominently the tendency of such relatively unstable tissue to revert to the simple embryonic type, to lose its acquired functions and retain its hereditary one of simple growth, and in that growth to preserve all the peculiarities of the great group of connective tissues to which it really belongs.

This study shows also, I think, the value of the embryological basis of the classification of tumors.

As a final word, but really as a statement of a preliminary thought, I thank Dr. Adami for his untiring interest in my work.

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NOTES ON NEW BOOKS.

An Introduction to Physiology. By WILLIAM TOWNSEND PORTER, M. D., Associate Professor of Physiology in the Harvard Medical School. Part IV—Physiological Optics. (*Cambridge, Mass.: The University Press, 1902.*)

A note of a preceding portion of Porter's Introduction to Physiology has already appeared in a former BULLETIN. This little primer of 93 pages contains much clear information and seems especially adapted to the use of students who are compelled to teach themselves with simple apparatus at home. A student who had personally conducted the series of experiments set down in this book would unquestionably enter upon the further laboratory study of the physiology of optics with a clearness of perception which would be most helpful.

The Principles of Bacteriology: A practical manual for Students and Physicians. By A. C. ABBOTT, M. D., Professor of Hygiene and Bacteriology and Director of the Laboratory of Hygiene, University of Pennsylvania. Sixth edition, enlarged and thoroughly revised, with 111 illustrations of which 26 are colored. (*Philadelphia and New York: Lea Brothers & Co., 1902.*)

The value of this book is well attested by the appearance of a sixth edition within ten years. It is probably the best manual we have for the class room and the prompt revision which it receives renders it modern and full of interest to the student. The first thirteen chapters furnish full and detailed instruction as to bacteria, their mode of multiplication and spore-formation, the principles of sterilization, methods for the isolation and cultivation of bacteria, methods of staining bacteria and finally their behavior when introduced into the animal body. The latter half of the work treats of the application of the methods of bacteriology to the study of disease and gives a description of special pathogenic organisms. We are gratified to see that the newer work in dysentery receives ample notice and that justice is done to the work of Shiga, Flexner and others. The book is practical and modern and deserves the success which it has attained.

Medical Lectures and Aphorisms. By SAMUEL GEE, M. D. (*Smith, Elder & Company, London, 1902.*)

This little book, containing fourteen medical lectures and two hundred and seventy-one aphorisms by Dr. Gee, must be of great interest to his students, since the collection doubtless contains those most characteristic of this eminent physician. Others will find the chapters, although few, brief, and disconnected, very suggestive and interesting.

Practical Dietetics. With Special Reference to Diet in Disease. Second edition. By W. GILMAN THOMPSON, M. D. (*D. Appleton & Company, New York, 1902.*)

This is a much-needed book and well fulfills the object for which it was intended. It is doubtless true that few physicians consider much the chemistry or the physiology involved in the nourishment of a patient by a given diet, much less the mathematics; yet these are quite as worthy of attention as are the chemistry, physiology, and knowledge of doses involved in writing a prescription.

The book contains a surprising amount and is written in an interesting manner. It discusses thoroughly foods and food preparations, their preparation, administration and physiologi-

cal value. The largest and best part deals with the diet in disease, and it would seem that no disease escaped an exhaustive discussion. The chemical and physiological paragraphs contain doubtless all that is essential, yet it is disappointing that the phraseology of these sciences is not more carefully followed, for the use of popular expressions often leads one to read the sentence again to make sure a popular error has not also been accepted.

The book is an excellent one and heartily to be recommended.

Climates and Baths of Great Britain and Ireland. The Climates of London and of the Central and Northern Portions of England. Together with those of Wales and Ireland. Vol. II. (*Macmillan & Company, London, 1902.*)

This large volume contains reports on the climates of certain districts of England, Wales and Ireland. Of these districts the various watering places or health resorts are described, their geographical, meteorological characteristics, drainage, water supply, etc., being presented. Then are given the Prevalence of Disease, the Frequency of Old Age and Common Causes of Death, and the Therapeutical Effect of the Climate. Each of these and many kindred subjects are discussed at length. The object of the volume is to aid the practitioner in choosing a suitable resort for his patient. The book contains many charts and tables.

A Practical Manual of Insanity. For the Student and General Practitioner. By DANIEL R. BROWER, A. M., M. D., LL. D., Professor of Nervous and Mental Diseases in Rush Medical College, and in the Post-Graduate Medical School, Chicago; and HENRY M. BANNISTER, A. M., M. D., formerly Senior Assistant Physician, Illinois Eastern Hospital for the Insane. 426 pages, with a large number of full-page inserts. Cloth, $3 net. (*Philadelphia and London: W. B. Saunders & Company, 1902.*)

"It is the aim of this work to present to the medical student and the general practitioner the essential aspects of mental disease as they have appeared to the authors. It is hoped that it will be found to give an intelligible, up-to-date statement of the leading facts and one that will be serviceable to those who may not be able to give the time for any more exhaustive study. . . . The work is intended for a handy manual for students; therefore elaborate case records and pathologic details, as well as discussions of speculative and controverted questions, are necessarily omitted. To make it the more practical and useful, certain special features are included, such as the mention of the forms of insanity not usually met with in hospitals for the insane, a comparative table of classification, and a chapter on some of the ethical questions relating to insanity as they may arise in the practice of medicine."

The above statement from the preface disarms much criticism. Viewed from the standpoint of the student and general practitioner the manual of Drs. Brower and Bannister is admirable, and they have fully succeeded in presenting the subject of insanity in a clear and concise manner. The authors have very wisely not restricted themselves to any one classification and have therefore given themselves greater freedom to treat of conditions rather than so-called entities. It is perhaps to be regretted that there should be quite so much brevity in the descriptions of the pathology of certain diseases. It does not seem that any clearness would be sacrificed in giving pathologic details where they are well known and the value of the book would be enhanced to the more advanced student. The description on pages 246-7 of the pathologic anatomy of paresis, while otherwise good in so far as it goes, makes but brief mention of the microscopic changes, omitting any detailed description of the nerve cell or any mention whatever of the disappearance of the tangential fibres. It is presumed that the statement on page 232, that "Its (paresis) period of greatest frequency is in the fourth and fifth decades of life, it is rare after fifty," should read its period of greatest frequency is in the third and fourth decades of life, etc. Lapses such as this are rare, however. The descriptions of insanity are admirable, and especially to be commended is the chapter on "Borderland and Episodic States," where the authors have handled a difficult subject most successfully.

Saunders' Question Compends; Essentials of Diseases of the Ear. By E. B. GLEASON, S. B., M. D., Clinical Professor of Otology, Medico-Chirurgical College, Philadelphia; Surgeon in charge of the Nose, Throat and Ear Department of the Northern Dispensary, Philadelphia, etc. Third edition, thoroughly revised. 16mo volume of 214 pages, with 114 illustrations. Cloth, $1 net. (*Philadelphia and London: W. B. Saunders & Co.; and Baltimore: Medical and Standand Book Co., 3 W. Saratoga St.*)

As a matter of preparing for an examination or to make a hasty review of a subject, these Quiz Compends are very useful to the student. This one covers the subject of otology completely and in a thoroughly satisfactory manner. The most important part of each topic is emphasized by a direct question and the answers bring out in a striking way the modern treatment thereof. The illustrations are apt and aid materially in a clear presentation of the matter.

H. O. R.

Treatise on Diseases of the Skin. For the use of Advanced Students and Practitioners. By HENRY W. STELWAGON, M. D., Ph. D. With 220 illustrations in the text and 26 full-page lithographic and half-tone plates. 8vo, 1115 pp. (*Philadelphia and London: W. B. Saunders & Company, 1902.*)

This is the best complete text-book on dermatology that we have at the present time; it is up to date in all departments and presents many new and valuable features not found in any other work on this subject.

Dr. Wm. M. Welch of the Municipal Hospital, Philadelphia, has written the papers on smallpox, scarlet fever and measles.

The usual chapters on anatomy and physiology of the skin are short but concise and adequate.

Symptomatology is given careful consideration. In order that the student may become well grounded in the rudiments, the primary and secondary lesions of the skin are described in detail. The clinical descriptions of the various diseases are, with a very few exceptions, well written, and the symptoms presented in such a clear and consecutive manner that the student readily grasps the essentials of a disease and easily follows its evolution.

The numerous, well selected and clear photographs aid one in remembering the general appearance of an eruption. Some colored plates have been taken from Mraček Hand Atlas, but they do not compare with the photographs in excellence and it is a question whether they strengthen this feature of the book.

Etiology and Pathology present the various theories and observations of the last 25 years. The views are, necessarily, varied, but will not confuse a careful reader. Numerous illustrations from the drawings of the best workers in this branch of cutaneous medicine enhance the value of this section.

The importance of an accurate diagnosis for the successful treatment of a disease is impressed upon the reader. Many suggestions mentioned in the chapter on General Diagnosis are

simplified and explained in differentiating the various dermatoses and prove of much value. An interesting section under this heading is the one giving Duration, Distribution, Character and Conspicuous Feature of an eruption as a diagnostic factor, although much clearness has been lost on account of lack of space given.

The materia medica and methods of treatment are taken up in detail. The recommendations offered are modern and should prove of value to the practitioner.

A supplementary and well-illustrated section deals with those diseases of adjoining mucous membranes not previously considered.

A most helpful feature to advanced students and dermatologists, and one showing the exacting labor of the author, is the reference bibliography given under each disease.

The British Guiana Medical Annual, Georgetown, Demerara. 8vo, pp. 84 + xxvi. 1902.

While this volume contains no extensive articles, it does contain a number of facts of interest in connection with the subject of tropical medicine. "Filarial lymphangitis" is discussed briefly by G. C. Low, while C. P. Kennard publishes some short "Notes on *Filaria* in birds," and Ozzard gives a "Description of a female parental form of the *Filaria Demarquayi*." Four articles appear on anchylostomiasis or uncinariasis, by Delamare, Ozzard (two articles), and Kennard, the most interesting points being that Delamare reports a blue-black pigmentation of the tongue in 17 cases and considers this an early sign of infection, while Ozzard supports Giles' view that *Uncinaria duodenalis* is subject to a heterogenesis in its development. Ozzard maintains that the free sexual stage develops in 8 to 10 days, and in the free female the eggs are arranged differently from those in *Strongyloides stercoralis*, appearing in one row instead of two; further, the embryo of *Strongyloides stercoralis* develops only in foul water and dies rapidly in decomposing feces, while the rhabditis of *Uncinaria duodenalis* develops best in decomposing feces; again, *Str. stercoralis* comes to maturity in 2 to 3 days, while *Uncinaria* takes at least 8 to 10 days. Ozzard's statements are interesting, but his illustrations are very poor and it is difficult to escape the feeling that his views should be taken with some reserve. It does not appear to be excluded, for instance, that both Giles and Ozzard have been dealing with a rhabditis which is related neither to *Uncinaria* nor to *Strongyloides*.

Daniels and Ozzard publish short papers on malaria, Kennard discusses fever cases, Carter describes three cases of beri-beri, Conyers gives an account of a case of hepatic abscess, de Freitas writes on a case of extrauterine gestation with passage of the fetal remains per rectum, Wishart discusses the influence of rainfall on the death-rate in the tropics, Raleigh has a short paper on anthrax in British Guiana, and the volume ends with The Transactions of the British Guiana Branch of the British Medical Association for the years 1900 and 1901.

Records of the Egyptian Government School of Medicine. Edited by the Director. Pp. 251. (*Cairo: National Printing Department, 1901.*)

Prof. Arthur Looss's article on "The Sclerostomidæ of horses and donkeys in Egypt" is one of the best papers on parasites which has ever been printed, if we view the work from the anatomical standpoint. The illustrations are excellent and, like other work by the same author, they set a high standard which probably few investigators can attain. Like other works by Looss, however, this paper is open to one rather severe criticism, namely, there is no analytical key to the numerous forms discussed. As a result it is necessary to read page after page before one finds just the data desired.

Professor William H. Wilson writes "On the poison of spiders with special reference to that of *Chatopelma olivacea*," concluding that the secretion of the poisonous glands is a viscid fluid of pale yellow color, acid reaction, and hot bitter taste; its physiological effect is apparently similar to curare, causing paralysis of the voluntary muscles, death resulting from the stoppage of the respiratory movements; watery extracts of the glands lose their toxic character upon being subjected to 60° C., and the activity of the venom is destroyed by putrefaction.

Professor Wilson also writes briefly "On the blood of *Chatopelma olivacea* with special reference to the presence of *Hæmocyanin*."

STUDIES IN TYPHOID FEVER.

SERIES I-II-III.

The papers on Typhoid Fever, edited by Professor William Osler, M. D., and printed in Volumes IV, V and VIII of The Johns Hopkins Hospital Reports have been brought together, and bound in cloth.

The volume includes thirty-five papers by Doctors Osler, Thayer, Hewetson, Blumer, Flexner, Read, Parsons, Finney, Cushing, Lyon, Mitchell, Hamburger, Dobbin, Camac, Gwyn, Emerson and Young. It contains 776 pages, large octavo with illustrations. It gives an analysis and study of the cases of Typhoid Fever in The Johns Hopkins Hospital for the past ten years.

The price is $5.00 per copy. Only a few copies of the volume are on sale. Those wishing to purchase should address their orders to the JOHNS HOPKINS PRESS, BALTIMORE, MARYLAND.

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GENERAL STATEMENT.

The Medical Department of the Johns Hopkins University was opened for the instruction of students October, 1893. This School of Medicine is an integral and coördinate part of the Johns Hopkins University, and it also derives great advantages from its close affiliation with the Johns Hopkins Hospital. The required period of study for the degree of Doctor of Medicine is four years. The academic year begins on the first of October and ends the middle of June, with short recesses at Christmas and Easter. Men and women are admitted upon the same terms.

In the methods of instruction especial emphasis is laid upon practical work in the Laboratories and in the Dispensary and Wards of the Hospital. While the aim of the School is primarily to train practitioners of medicine and surgery, it is recognized that the medical art should rest upon a suitable preliminary education and upon thorough training in the medical sciences. The first two years of the course are devoted mainly to practical work, combined with demonstrations, recitations and, when deemed necessary, lectures, in the Laboratories of Anatomy, Physiology, Physiological Chemistry, Pharmacology and Toxicology, Pathology and Bacteriology. During the last two years the student is given abundant opportunity for the personal study of cases of disease, his time being spent largely in the Hospital Wards and Dispensary and in the Clinical Laboratories. Especially advantageous for thorough clinical training are the arrangements by which the students, divided into groups, engage in practical work in the Dispensary, and throughout the fourth year serve as clinical clerks and surgical dressers in the wards of the Hospital.

REQUIREMENTS FOR ADMISSION.

As candidates for the degree of Doctor of Medicine the school receives:

1. Those who have satisfactorily completed the Chemical-Biological course which leads to the A. B. degree in this university.

2. Graduates of approved colleges or scientific schools who can furnish evidence: (a) That they have acquaintance with Latin and a good reading knowledge of French and German; (b) That they have such knowledge of physics, chemistry, and biology as is imparted by the regular minor courses given in these subjects in this university.

The phrase "a minor course," as here employed, means a course that requires a year for its completion. In physics, four class-room exercises and three hours a week in the laboratory are required; in chemistry and biology, four class-room exercises and five hours a week in the laboratory in each subject.

3. Those who give evidence by examination that they possess the general education implied by a degree in arts or in science from an approved college or scientific school, and the knowledge of French, German, Latin, physics, chemistry, and biology above indicated.

Applicants for admission will receive blanks to be filled out relating to their previous courses of study.

They are required to furnish certificates from officers of the college or scientific schools where they have studied, as to the courses pursued in physics, chemistry and biology. If such certificates are satisfactory, no examination in these subjects will be required from those who possess a degree in arts or science from an approved college or scientific school.

Candidates who have not received a degree in arts or in science from an approved college or scientific school will be required (1) to pass, at the beginning of the session in October, the matriculation examination for admission to the collegiate department of the Johns Hopkins University, (2) then to pass examinations equivalent to those taken by students completing the Chemical-Biological course which leads to the A. B. degree in this University, and (3) to furnish satisfactory certificates that they have had the requisite laboratory training as specified above. It is expected that only in very rare instances will applicants who do not possess a degree in arts or science be able to meet these requirements for admission.

Hearers and special workers, not candidates for a degree, will be received at the discretion of the Faculty.

ADMISSION TO ADVANCED STANDING.

Applicants for admission to advanced standing must furnish evidence (1) that the foregoing terms of admission as regards preliminary training have been fulfilled, (2) that courses equivalent in kind and amount to those given here, preceding that year of the course for admission to which application is made, have been satisfactorily completed, and (3) must pass examinations at the beginning of the session in October in all the subjects that have been already pursued by the class to which admission is sought. Certificates of standing elsewhere cannot be accepted in place of these examinations.

SPECIAL COURSES FOR GRADUATES IN MEDICINE.

Since the opening of the Johns Hopkins Hospital in 1889, courses of instruction have been offered to graduates in medicine. The attendance upon these courses has steadily increased with each succeeding year and indicates gratifying appreciation of the special advantages here afforded. With the completed organization of the Medical School, it was found necessary to give the courses intended especially for physicians at a later period of the academic year than that hitherto selected. It is, however, believed that the period now chosen for this purpose is more convenient for the majority of those desiring to take the courses than the former one. The special courses of instruction for graduates in medicine are now given annually during the months of May and June. During April there is a preliminary course in Normal Histology. These courses are in Pathology, Bacteriology, Clinical Microscopy, General Medicine, Surgery, Gynecology, Dermatology, Diseases of Children, Diseases of the Nervous System, Genito-Urinary Diseases, Laryngology and Rhinology, and Ophthalmology and Otology. The instruction is intended to meet the requirements of practitioners of medicine, and is almost wholly of a practical character. It includes laboratory courses, demonstrations, bedside teaching, and clinical instruction in the wards, dispensary, amphitheatre, and operating-rooms of the Hospital. These courses are open to those who have taken a medical degree and who give evidence satisfactory to the several instructors that they are prepared to profit by the opportunities here offered. The number of students who can be accommodated in some of the practical courses is necessarily limited. For these the places are assigned according to the date of application.

During October a select number of physicians will be admitted to a special class for the study of the important tropical diseases met with in this region.

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